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Automatic Electronic Computer for the Estimation of Arterial Concentration of Evans Blue Dye

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INTRODUCTION

Measurement of cardiac output according to the method of Hamilton and associates has been greatly facilitated through the introduction of techniques and apparatus for continuous recording of the dye concentration in the arterial blood. Particular effort has been directed toward the development of photoelectric techniques. Ear and whole blood oximeters and various types of densitometers have been skillfully and successfully employed by different workers for recording the dye dilution curves.*

In order to make the dye dilution curves quantitative in all these methods, it is necessary to obtain one or more calibrating samples of either arterial or venous blood in each subject. With the cuvette and ear oximeter[1-4] and densitometers[5-7] the standardization is accomplished by measuring the changes in optical density produced by adding known amounts of dye to the venous blood samples, withdrawn from the subjects prior to the injection of dye. In the "one point" method of calibration[8] using the ear densitometer the calibration of each individual dilution curve is achieved by drawing the venous blood sample a few minutes after the injection of dye and estimating the plasma dye concentration photometrically.

The purpose of this paper is to describe a method which was developed in an attempt to eliminate the technically difficult and tedious collection and analysis

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*Recently, Dow published a detailed historical and critical review on this subject.[15]

of calibrating samples by providing a direct estimation of dye concentration in the arterial blood, and thus to simplify greatly the measurement of cardiac output.

As a result of extensive experience gained in the course of the past few years in designing and using ear and whole blood oximeters, the construction of an automatic computing ear oximeter* was undertaken with the thought that, if it proved feasible to compute the arterial oxygen saturation with sufficient accuracy by automatic electronic means, then the same device might be employed to compute the concentration of the dye T-1824 in the arterial blood.

The main reasons for constructing such an instrument have been as follows: (1) Collection and photometric analysis of arterial or venous blood samples for the purpose of calibrating individual dye dilution curves could be avoided. (2) In addition to a considerable saving of labor and time, pain and discomfort to the patients could be greatly reduced because only one venous puncture for injection of dye would be required. (3) The use of a single calibrating factor applicable to all subjects would simplify the procedure and also provide an accurate estimation of the cardiac output. (4) The source of error due to inaccuracies in the photometric determinations of the plasma dye concentration, when not carried out with extreme care and by a highly trained person, would be eliminated. (5) Since there is no waiting required between the time of injection and the sampling, the hazards of wavering in the base line, due to changes in the condition of the patient or to instability of the recording system, would be greatly reduced.

The foregoing considerations deserve particular attention when multiple injections with relatively small doses of dye are performed in infants or in small children, because it is difficult, if not impossible, to maintain the children in the steady state for the required period without a high degree of sedation or anesthesia.

METHOD AND APPARATUS

Nicholson and Wood[1] first employed oximetric methods for photometric estimations of Evans blue T-1824 dye. They observed that this dye, like reduced hemoglobin, increases the red light absorption (about 640 mμ), but has small effect on the infrared light (about 800 mμ). Based on this observation, the method for direct estimation of the T-1824 concentration to be described is similar to that used by us to determine the absolute value of the arterial oxygen saturation by means of an ear oximeter. Detailed description of the principles involved, and construction and mode of operation of this instrument have been reported previously.[9,10] Its main features are summarized as follows: (1) The absolute value of the oxygen saturation may be obtained without the necessity of excluding the blood by pressure from the heat-flushed ear. (2) The circuit arrangement represents basically a null method. (3) A bias cell is used and a dial scale serves as an accurate means to measure the bias current which flows in the circuit. (4) When, by rotation of the dial, the red photocurrent is balanced against the bias current, the scale reading is a precise measure of the output of the red photocell. (5) A built-in double-beam galvanometer is employed, one beam of which—the red (upper scale)—serves as the null instrument, while the other (lower scale) measures the infrared photocurrent. (6) The oximeter can be calibrated with optical filters without the necessity of comparisons against manometric determinations on arterial samples. (7) The percentage of oxygen saturation is obtained from the oximeter

*The instrument to be described was developed as a joint project of the Department of Physiology, McGill University, and the Department of Cardiology, The Montreal Children's Hospital.

readings by means of a manually operated calculator which performs the computation of the ratio: $\frac{\log R - \log R_x}{\log R_1 - \log k \cdot IR}$ (Ref. 9, Equation 7a, p. 843). In this expression R and $R_x = R - \Delta R$ refer to the galvanometer deflections obtained with the red filtered photocell at two different levels of oxygen saturation; ΔR represents the amount by which the galvanometer deflection decreases when the oxygen saturation decreases. IR refers to the galvanometer deflection obtained with the infrared filtered photocell. R_1 may be obtained by direct measurement in normal subjects when breathing room air or oxygen or may be calculated from the relationship:

$$R_1 = m \times \log Hb \times (IR\text{-}a)$$

(see Ref. 10, p. 757) where m and a are apparatus constants and Hb is the hemoglobin concentration in grams per 100 ml. In subjects with arterial unsaturation R_1 should be calculated from this expression. The circuit is so arranged that k = 1 when 1 scale division = 4.55 mm. galvanometer deflection.

The arterial dye concentration is calculated from the following relationship:

$$\text{Dye concentration} = K \frac{\log R - \log R_x}{\log R_1 - \log IR} \qquad (1)$$

which is similar in form to that noted above for the computation of the arterial oxygen saturation. Here, R and R_x refer to the galvanometer deflections obtained with the red filtered photocell, before and after injection of dye, respectively. R_1 and IR have the same meaning as indicated above, and K is an empirical calibration constant.

The automatic and continuous computation of the dye concentration is accomplished in the following manner: the optical density of the ear is measured continuously in the red and infrared absorption bands. Before the injection of dye when, by rotating the oximeter dial, balance is established between the bias current, designated by C, and the red photocurrent R, the value of Equation 1 is equal to zero, since $R = R_x$. After the injection of dye, while C remains constant, the optical density of the ear increases in the red (R_x decreases) and remains unchanged in the infrared (IR unaffected). Since the galvanometer deflection bears a logarithmic relationship to the optical density, the logarithm of R_x should be subtracted from the logarithm of C and this operation is performed automatically. Simultaneously, this difference is divided by the value of the "ear thickness": $\log R_1 - \log IR$ by automatic electronic means.

The functional block diagram of the instrument is shown in Fig. 1. The earpiece light source is a 6- to 8-volt flashlight bulb operated at 5.25 volts either from a storage battery or from a regulated direct current power supply. The red and infrared radiations are obtained by employing one layer of Wratten 29 and two layers of Wratten 87 gelatin filters, respectively.

The action of the circuit is as follows: the potentials developed by the photocells are impressed upon the oximeter circuitry (Ref. 10, p. 749). The voltage signals appearing at the output terminals of the oximeter are converted by means of 60 c.p.s. choppers into square waves which are amplified by resistance-capacitance coupled push-pull amplifiers and finally rectified. These voltages, e_r and e_i are measured by vacuum tube voltmeters,* and simultaneously impressed on a half section of logarithmic-taking bridge circuits. Upon the input terminals of the other half section of these circuits, a voltage e_c is impressed, the value of which is determined by the setting of the main dial of the oximeter. This setting may be accomplished in two different ways: (1) In normal subjects breathing room air or oxygen the value of variable e_{r1} (corresponding to R_1 in Equation 1) is automatically established, since $e_{r1} = e_r = e_c$ before the injection of dye and the

*From the point of view of design, the gain and zero line stability of the amplifying system were of considerable concern. After a preheating period of about 30 minutes, the zero drift of the vacuum tube voltmeters used is well within 1μV./hour, as referred to the input, which is less than 1 per cent of the full-scale deflection sensitivity. In order to duplicate exactly the calibration characteristics and the established instrument constants of the oximeter, the gain controls are so adjusted that readings taken with both vacuum tube voltmeters and galvanometer (standard) are identical. Although there is no need for the external galvanometer to be used during routine operation, it was employed during the calibration studies to check the zero line stability of the system and the accuracy of the readings. By means of simple switching, readings can be taken with either the galvanometer or with the vacuum tube voltmeters.

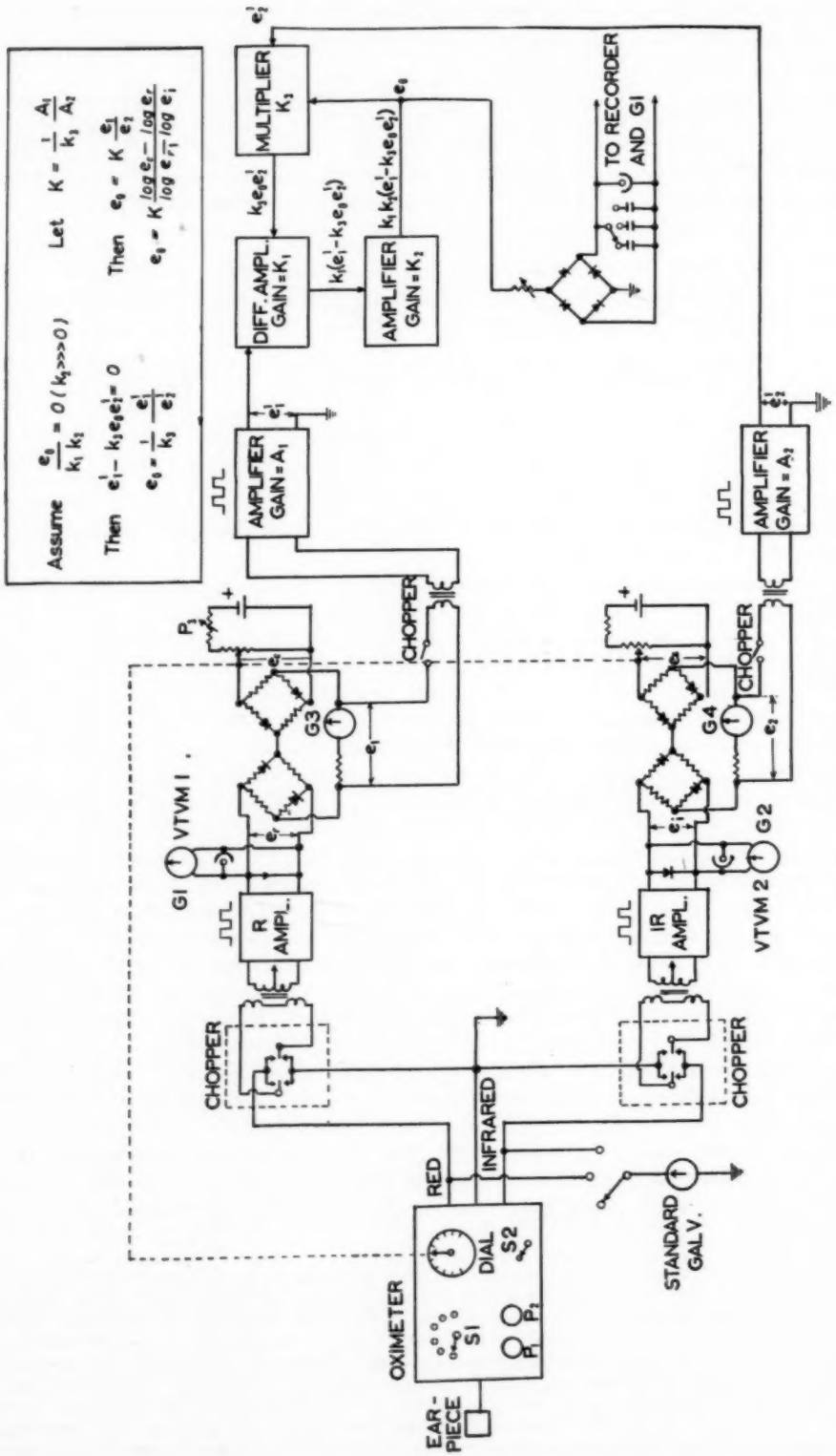

Fig. 1.—Functional block diagram.

condition of the bridge balance, in the red channel, is indicated by the zero position of the meter G_3. (2) In subjects with arterial unsaturation and in nonwhite subjects the value e_{r1} has to be calculated from the relationship $e_{r1} = m \times \log Hb \times (e_i - a)$, and introduced separately into the computing system. This is accomplished by setting the dial scale to the corresponding value of e_{r1}, calculated from this expression. By doing this the balance between e_o and e_r is disturbed, since $e_{r1} > e_r$. The bridge circuit is then rebalanced by zeroing the meter G_3 with the help of the variable resistance P_3. The logarithmic bridges are made up of selenium rectifiers and resistors. Their outputs are connected in series, and fed with opposite sign, to a meter which reads the difference of their output currents. The voltage drops across the meters, G_3 and G_4, and the series connected resistors are: $e_1 = B_1 (\log e_c - \log e_r)$ and $e_2 = B_2 (\log e_c - \log e_i)$, where B_1 and B_2 are constants.

The voltages e_1 and e_2 are chopped at the rate of 60 c. p. s. by a pair of different choppers, and the resulting square wave voltages are amplified by single ended resistance-capacitance coupled amplifiers of gain A_1 and A_2, respectively. The outputs $e_1' = A_1 \cdot e_1$ and $e_2' = A_2 \cdot e_2$ are now fed into an electronic computer which performs the operation $\frac{e_1'}{e_2'}$ according to the method[11] indicated in the insert of the block diagram. The computer output is a square wave of amplitude $e_o = K \frac{e_1'}{e_2'}$, where K is a factor of proportionality. Finally, e_o is rectified and read off the scale of the meter G_1, and simultaneously recorded with one of the galvanometers of a direct-writing pen recorder (Sanborn Model 150).

In order to compare the automatically computed values of the dye concentration with those obtained by point-by-point calculations from individual oximeter readings, the voltages e_r and e_i are separately recorded with the direct-writing recorder.

OPERATION

Referring to the basic switching circuit shown in Fig. 2 and the photograph shown in Fig. 3, the standardization is accomplished in the following manner: one of the filters of a rotating problem chart (shown in the upper left corner of Fig. 3), which incorporates nine standard filters of known optical densities, is inserted into the earpiece. With the operation selector switch S_1 in the first position and the switch S_2 off, the red V.T.V.M. (vacuum tube voltmeter) is zeroed and the infrared V.T.V.M. is offset to full scale deflection. S_2 is then turned to the "on" position and the calibrating signals are impressed upon the inputs of the amplifiers. By means of the amplifier gain controls, the V.T.V.M. and the meter G_3 in the red channel are brought to full scale deflection, while the V.T.V.M. and the meter G_4 in the infrared channel are zeroed. S_1 is next turned to the second position and the dial scale is set to a definite value, depending upon the standardization filter present in the light path. Balance between the voltages e_c and e_r is established by zeroing the red V.T.V.M. with the help of the red photocell sensitivity control P_1. Following this, the infrared photocell sensitivity control P_2 is so adjusted that a definite reading is obtained with the infrared V.T.V.M. With the dial scale remaining in the preset position, S_1 is turned to the third position and the red bridge circuit is balanced by zeroing the meter G_3 by means of the variable resistance P_3. In the fourth and fifth positions of S_1 the meter G_1 is zeroed in order to provide proper grid bias voltages for the multiplier tube of the computing circuit. Finally, in the sixth position of S_1 the meter G_1, the scale of which is calibrated in per cent oxygen saturation, is connected to the output of the computer. Assuming the procedure has been carried out properly with the standardization filter in the earpiece, the scale reading will be between 98 and 99 per cent oxygen saturation. If one or more of the standard filters of increasing optical density are now successively positioned in the light path, decreases in oxygen saturation are simulated and recorded on the saturation scale. A fine control is provided to adjust the computer output when the readings differ by more than ± 2.5 per cent, in the range of 50 to 100 per cent, from the predicted values of the simulated oxygen saturation.

As soon as the standardization procedure has been completed, S_1 is turned back to the first position and the earpiece is fitted onto the pinna. S_1 is then turned to the second position and by rotating the dial in either direction, depending upon the characteristics of the individual ear,

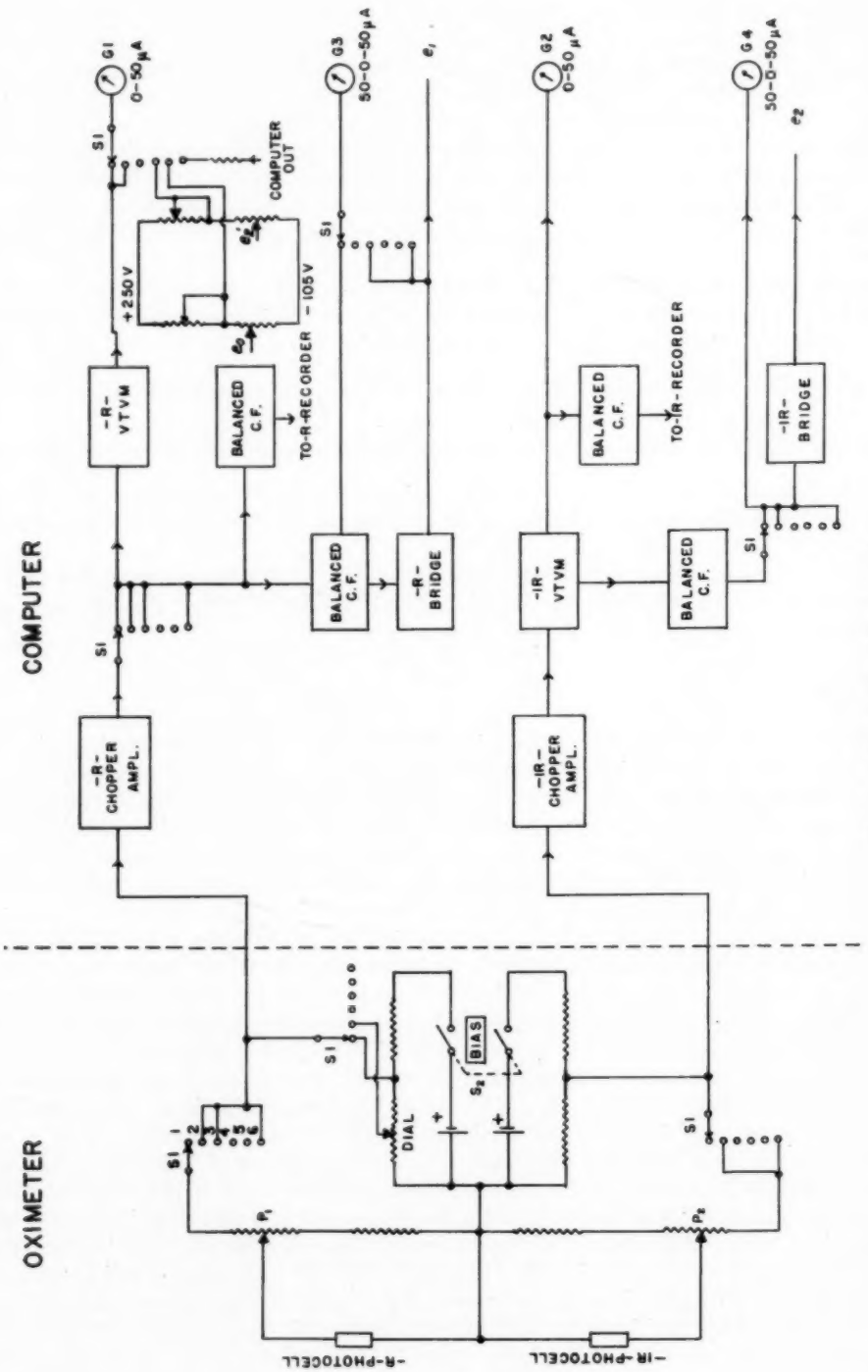

Fig. 2.—Basic switching circuit.

the deflection of the red V.T.V.M. is restored to the zero position. Readings are taken in this position until the meter readings are constant, indicating that the ear is fully flushed. S_1 is then turned to the sixth (computing) position. The direct recording system is next turned on and the galvanometer base lines are positioned. When the base-line recordings appear to be stable over a short period of about 30 to 60 seconds, the dye is quickly injected. Soon after the dye dilution curve has been inscribed, S_1 is turned to the first position and the initial zero settings of the system are checked. A waiting period of about 5 minutes is required, to allow the dye concentration to reach equilibrium in the venous and arterial systems, before subsequent injections are performed. Compensation for the increase in optical density due to the presence of dye from the previous injection is achieved by so readjusting the dial that the deflection of the red V.T.V.M. is restored to the zero position (S_1 in position 2) and by rebalancing the meter G_3 (S_1 in position 3). In order to proceed with the next injection it suffices to turn S_1 into position 6 and to reposition the base lines of the recording galvanometers.

Sample records are shown in Fig. 4. Fig. 4,*A* is the record of two consecutive dye dilution curves obtained from a normal subject breathing oxygen, with about 0.2 mg./Kg. dye injected

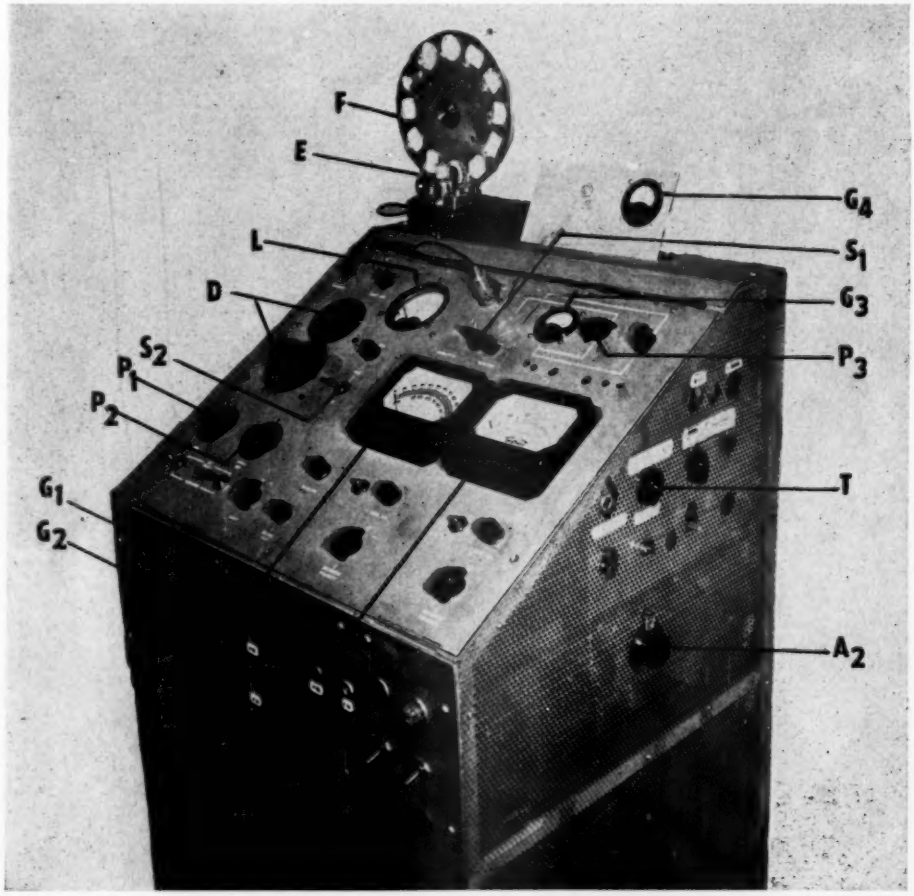

Fig. 3.—Photograph of the instrument. G_1, red V.T.V.M. G_2, infrared V.T.V.M. G_3 and G_4, bridge balance micro ammeters for the red and infrared channels, respectively. P_1 and P_2, red and infrared photocell adjust controls. P_3, red bridge balance control. A_1 (not seen) and A_2, gain controls for the red and infrared amplifiers, respectively. D, main dial scale. S_1, operation selector switch. S_2, bias cell on-off switch. L, light source intensity voltmeter with expanded scale. T, time constant selector switch. F, rotating problem chart. E, earpiece.

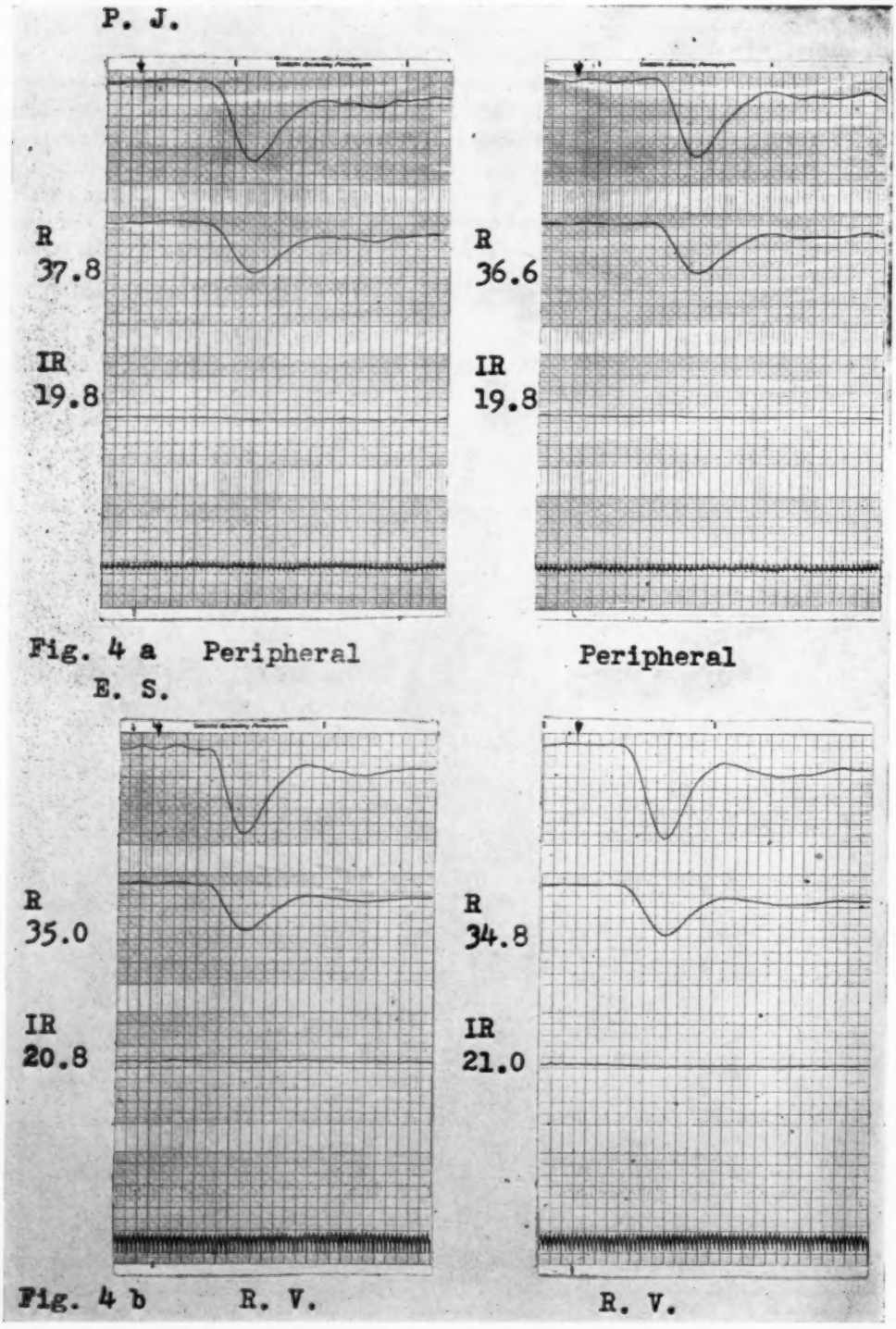

Fig. 4.—Dye dilution curve sample records. *A*, Dilution curves from a normal subject breathing room air, after peripheral injection of T-1824, about 0.2 mg./Kg. per injection. *B*, Dilution curves from a patient with valvular pulmonic stenosis, breathing room air. About 0.2 mg./Kg. of dye per injection was introduced into the right ventricle.

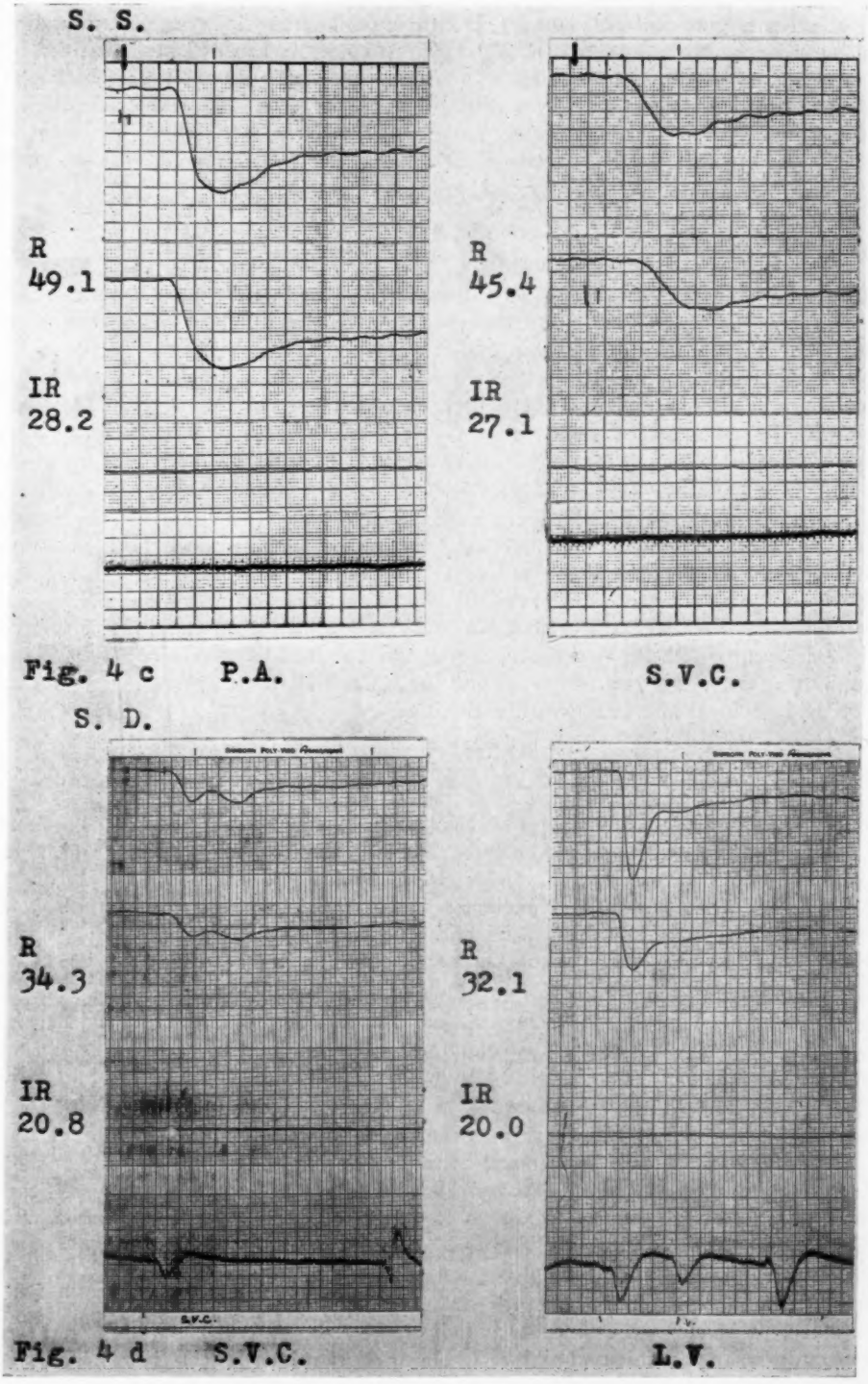

Fig. 4.—Cont'd. *C*, Typical dye dilution curves obtained from a patient with left-to-right shunt, breathing room air, after the injection of about 0.3 mg./Kg. of dye into the pulmonary artery and the superior vena cava, respectively. *D*, Dilution curves from a patient with right-to-left shunt at atrial level, breathing oxygen. The first curve shows the typical double hump when the dye was injected into the superior vena cava. The second curve is of normal contour when the injection site was at the left ventricle. The amount of injected dye was about 0.3 mg./Kg. for each injection. In all of these records the tracings from top to bottom are: the computer, the red channel, the infrared channel, and the ECG. The arrows indicate the time of injection. The writing speed is 2.5 mm./sec.

each time into the antecubital vein. Fig. 4,*B* shows 2 consecutive dye dilution curves obtained from a patient with pure pulmonic stenosis, breathing room air, by injecting each time about 0.2 mg./Kg. of dye into the right ventricle. The records shown in Fig. 4,*C* were obtained from a patient with left-to-right intracardiac shunt, breathing room air, when about 0.3 mg./Kg. of dye was injected into the pulmonary artery and into the superior vena cava, respectively. Fig. 4,*D* shows the tracings obtained from a patient breathing oxygen, with a right-to-left shunt at the atrial level. The first injection site was the superior vena cava and the second, the left ventricle. About 0.3 mg./Kg. of dye was used for each injection.

CALIBRATION

Calibration studies in vivo started only after carefully conducted control experiments, using various combinations of standard filters, had indicated that the stability and the sensitivity of the instrument were adequate for recording several, successive dye dilution curves with small quantities of dye (0.2 to 0.3 mg./Kg. per injection). The calibration consisted of correlating the values of the ratio in Equation 1, calculated from the separate recordings in the red and infrared channels, with the photometrically determined values of the plasma dye concentration of the blood samples withdrawn during the experiments. One aim of these studies was to avoid any procedure which involved arterial puncture for the purpose of calibration.

In spite of serious difficulties which may be experienced in different situations, the comparison between the values calculated from individual instrument readings and the photometrically determined values of the plasma dye concentration obtained in single venous blood samples (withdrawn 5 minutes after the injection of dye) appeared to be the most convenient procedure for calibration. The acetone extraction method[12] was used, with the Coleman junior spectrophotometer (concurrently with the Beckman spectrophotometer in some cases) for analysis. Two control samples containing dye concentrations of 5 mg./L. and 10 mg./L. plasma were prepared to construct the individual photometric calibration line.

To arrive at the greatest possible accuracy in constructing the correlation line between the photometric and oximetric estimations, the experiments were discarded when: (1) the photometric determinations yielded unsatisfactory results, (2) the interpretation of the amount of recorder deflection in the red channel, due to the dye, was obscured by the instability of the tracing during the sampling period. It should be noted, however, that the experiments in which changes in the base line were due to changes in the ear circulation were not necessarily excluded. It was mentioned earlier that an external galvanometer was used during the calibration studies to check the zero line stability of the instrument. Thus, when the circulation in the ear changed, this was indicated by the IR reading of the galvanometer and accounted for by considering it in Equation 1.

Fig. 5,*A* shows the calibration diagram which was obtained by plotting the photometrically determined values of the plasma dye concentration against the values of the ratio calculated from Equation 1. This diagram is based on 16 simultaneous determinations performed in 9 subjects, of whom 8 were normal subjects (6 white, 1 Indian, and 1 Chinese) and 1 was a child with pure pulmonic stenosis.

Fig. 5,*B* shows the calibration diagram of the computer. It was constructed by plotting the values of the plasma dye concentration read off the correlation line in Fig. 5,*A*, corresponding to the values of the ratio calculated from the instrument readings, against the deflections of the computer galvanometer at the point of maximum concentration of the dye dilution curves obtained in the 9 subjects.

It is of interest to note that the calibration lines depart from linearity in the low range of dye concentration. Unfortunately no calibrating samples in the very low range of dye concentration were obtained. Therefore, the contour, as indicated by the broken-line section of the graph, may be regarded as only an approximation. A linear relationship between the oximeter readings and the dye concentration reported by Gilmore and associates,[14] when using a Wood oximeter, could not be reproduced by our system. There is a close similarity between the deviation from linearity exhibited by this calibration curve and the deviation exhibited by those for oxygen saturation with ear and whole blood oximeters using identical type of filter-photocell combinations.

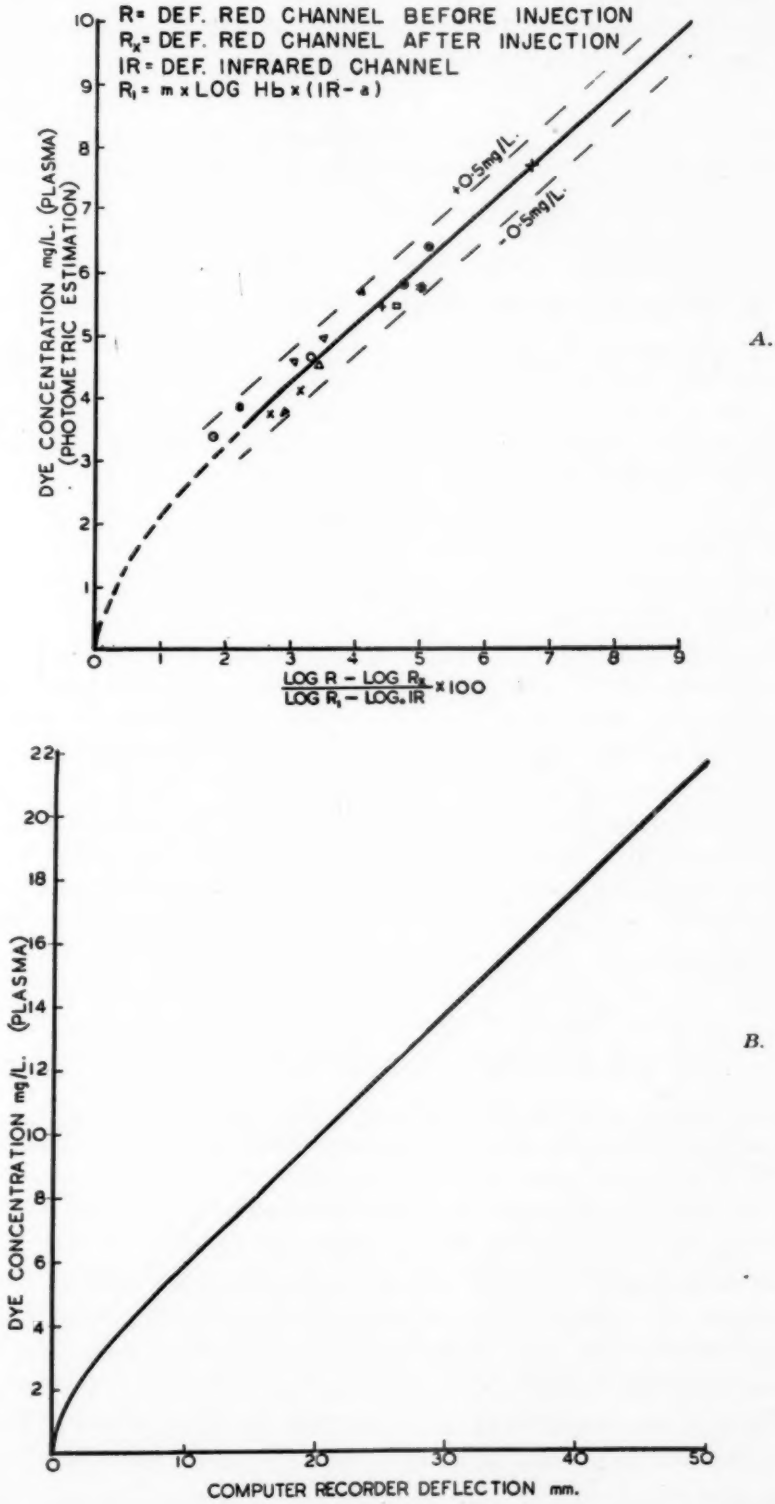

Fig. 5.—Calibration diagrams.

We have reported[13] that substitution of a narrow band interference filter for the gelatin filter in the red absorption band resulted in a straight-line relationship between the oxygen saturation values and the values calculated from the oximeter readings.

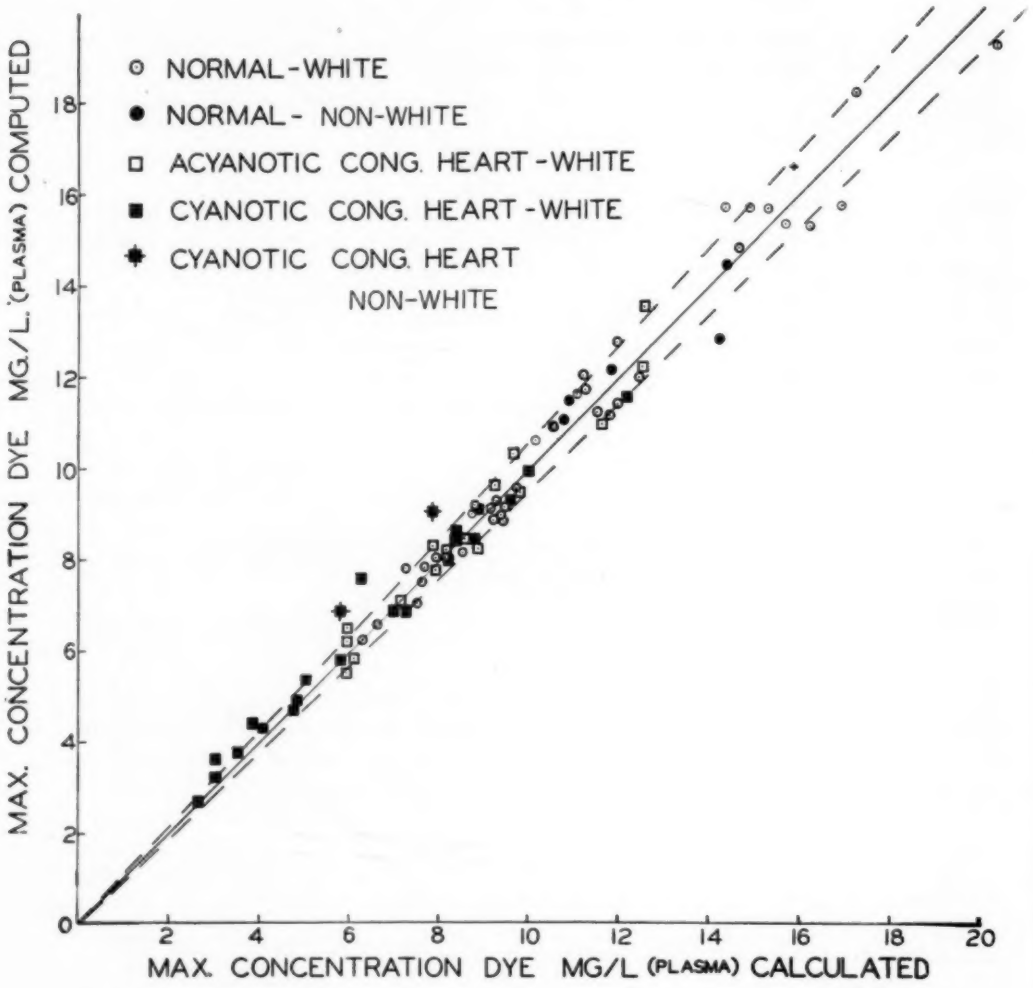

Fig. 6.—Comparison of the measurements of the maximum dye concentrations obtained by automatic computation and by calculation from individual instrument readings. (Non-white includes Negro, Chinese, and Indian.)

RESULTS

In order to assess the accuracy of the automatic computation, the maximum values of the dye concentration recorded by automatic means are compared with those obtained by calculation from the individual instrument readings. Eighty-one from 86 determinations in 35 subjects are shown in Tables I and II and in Fig. 6, which compare the computed and calculated values of the maximum dye concentration in normal subjects (Table I) and in subjects with congenital heart malformations (Table II). Sixteen subjects were normal young adults, in 3 of whom injections were made on two different occasions. Nineteen were

children between the age of 7 weeks and 14 years, with various cardiac malformations, in 1 of whom the injection was repeated at a later date. Five determinations were discarded because of unsuccessful injection and/or instability of the base line.

In the first 6 subjects in each group, radiant heat from the earpiece light bulb alone was used to produce vasodilation in the pinna. In the others, Trafuril* (5 per cent w/w tetrahydro furfuryl nicotinic acid ester in a water miscible base) was rubbed lightly into the skin of the ear about 20 minutes prior to attaching the earpiece to the pinna. Application of this vasodilator shortens the stabilization period and a steady base line is ordinarily obtained within minutes.

A satisfactory base line could be obtained in adult subjects without sedation after resting for 30 minutes, but in children a combination of Demerol and Nembutal, 2.2 mg. of each per kilogram of body weight, was given intramuscularly. Measured quantities of 0.5 per cent T-1824 were injected rapidly and followed immediately by a rapid injection of 5 c.c. of physiologic saline. Ordinarily, 5 to 7 minutes elapsed before the next injection.

In the normal adult group (Table I) with an average dose of 0.21 ± 0.01 mg./Kg. of dye per injection, the mean values of the maximum dye concentration in mg./L. plasma are 11.32 ± 1.01 (6.33-20.3) and 11.29 ± 1.00 (6.20-19.15) for the calculated and the computed values, respectively. The numbers following the ± signs are twice the standard error of the means, and the ranges are indicated by the numbers in the parentheses. The correlation between the calculated and the computed values is 0.986, and the standard deviation of the differences in mg./L. is 0.606. In the second group (Table II) with an average dose of 0.3 ± 0.03 mg./Kg. of dye per injection and the oxygen saturation varying from 63.0 to 99.5 per cent (Hb from 9.75 to 17.7 Gm./100 ml.), the mean values of the maximum concentration in mg./L. plasma are 7.36 ± 0.83 (2.46-12.65) and 7.50 ± 0.81 (2.66-13.58) for the calculated and the computed values, respectively.† The correlation is 0.993 and the standard deviation of the differences is 0.550 mg./L. plasma.

COMMENTS

The results reported here and others to be published in a paper on estimation of cardiac output by dye dilution indicate that photoelectric measurements based on the principles of oximetry allow quantitative determination of the dye concentration in the circulating arterial blood. The comparison between the results obtained in normal subjects and in those with cardiovascular anomalies suggests that a single calibrating factor may be established which is applicable to all subjects, independent of age or sex, pigmentation of skin, hemoglobin concentration and initial level of oxygen saturation varying within wide limits.

The adequacy of the system in recording small concentrations of dye is demonstrated by the deflection sensitivity of the computer galvanometer which

*Kindly supplied by the Ciba Company, Ltd., Montreal, Canada.

†The data pertaining to subject R. W. (No. 3 in Table II) are excluded from the statistical treatment because they greatly exceed the range of all the other determinations.

TABLE I. NORMAL SUBJECTS

NO.	DATE	SUBJECT	SEX	AGE (YR.)	P.C.V. (%)	OXIMETER READINGS BEFORE INJECTION		NUMBER	DYE INJECTED (MG./KG.)	MAXIMUM DEFLECTION (MM.)		MAXIMUM CONCENTRATION (MG./L.)		REMARKS
						R SCALE*	IR (MM.)			RED CHANNEL	COMPUTER	CALCULATED	COMPUTED	
1	10/25/55	A.D. (Indian)	M	28	48	27.3	20.2	1st	0.202	14.0	26.00	11.85	12.15	Quiet, breathing room air
						24.6	18.0	2nd	0.200	14.8	27.80	14.22	12.80	
2	10/31/55	W.J.	F	35	33	36.1	18.0	1st	0.196	21.8	23.20	11.80	11.10	Moderately quiet, breathing room air
						35.7	16.0	2nd	0.190	10.7	14.95	7.70	7.85	
3	11/ 1/55	S.F.	F	27	37	55.8	28.9	1st	0.248	12.7	10.70	6.33	6.20	Quiet, breathing room air
						53.2	28.6	2nd	0.248	18.8	18.10	9.38	9.08	
						53.5	28.0	3rd	0.208	14.4	14.80	7.29	7.80	
4	11/ 2/55	B.W. (Chinese)	M	28	45	31.3	19.6	1st	0.197	14.1	24.30	10.87	11.50	Quiet, breathing oxygen
						30.3	19.3	2nd	0.195	13.1	23.50	10.80	11.17	
						29.0	18.5	3rd	0.202	17.8	32.00	14.32	14.50	
5	11/22/55	W.M.	M	28	42	46.4	25.3	1st	0.197	17.8	17.50	9.30	8.90	Quiet, breathing oxygen
						42.7	22.1	2nd	0.202	16.7	19.20	9.77	9.50	
						42.1	22.0	3rd	0.196	12.1	14.00	7.65	7.50	
6	2/14/56	S.F.	F	27	34	48.3	25.3	1st	0.163	11.5	11.70	6.64	6.58	Quiet, breathing oxygen
						45.3	24.8	2nd	0.196	11.8	12.90	7.52	7.05	
						44.2	24.8	3rd	0.206	13.0	15.80	8.58	8.18	
7	2/15/56	G.R.	M	24	43	34.6	20.8	1st	0.192	13.5	24.20	12.04	11.46	Restless, breathing with difficulty
8	2/29/56	C.F.	M	35	43	28.6	17.2	2nd	0.398	12.8	32.70	14.70	14.77	Quiet, overbreathing slightly, oxygen
9	3/13/56	A.D. (Indian)	M	28	44	28.8	19.0	1st	0.180	13.0	18.20	9.20	9.10	
						27.7	18.6	2nd	0.183	12.0	18.30	9.27	9.15	Quiet, breathing oxygen
						26.7	17.8	3rd	0.194	11.9	17.70	9.40	8.92	

10	3/15/56	M.P.	F	25	37	53.1	28.1	1st	0.191	19.5	15.50	8.15	8.07	
						51.6	28.0	2nd	0.193	23.2	17.60	9.40	8.88	Quiet, breathing oxygen
						50.3	27.7	3rd	0.194	19.5	15.50	8.00	8.07	
11	3/20/56	M.W.	M	26	42	26.5	14.0	1st	0.198	22.2	42.80	17.20	18.15	Somewhat restless, breathing room air
12	4/10/56	R.P.	F	35	41	56.7	29.0	1st	0.146	31.7	26.00	11.23	12.16	
						52.6	27.0	2nd	0.184	31.5	27.50	11.95	12.75	Quiet, breathing oxygen
						50.7	26.3	3rd	0.196	28.0	25.00	11.33	11.77	
13	4/17/56	A.F.	F	28	36	46.0	23.6	1st	0.288	24.1	22.90	10.65	10.95	Apprehensive, breathing room air
						43.6	22.7	2nd	0.280	24.5	23.50	11.57	11.20	
14	5/29/56	M.W.	M	26	40	22.1	12.5	2nd	0.196	11.7	25.40	12.49	11.94	Restless, breathing oxygen
15	4/ 3/57	P.J.	M	30	44	37.8	20.1	1st	0.200	22.5	34.30	14.35	15.67	Quiet, breathing oxygen
						36.6	19.8	2nd	0.210	23.0	34.80	15.30	15.64	
16	4/ 9/57	R.O.	M	30	42	24.4	14.8	1st	0.212	17.8	44.00	20.30	19.15	Quiet, breathing room air
						24.2	14.8	2nd	0.209	14.1	34.75	16.90	15.70	
17	4/12/57	J.Y.	F	44	41	38.2	21.8	1st	0.210	23.5	35.00	14.90	15.65	Quiet, breathing oxygen
						36.9	21.7	2nd	0.208	14.5	22.00	10.15	10.60	
18	4/12/57	E.S.	F	24	37	36.4	20.3	1st	0.201	13.0	18.30	8.85	9.25	Quiet, breathing room air
						34.9	20.1	2nd	0.189	15.0	24.50	11.05	11.60	
19	5/ 7/57	P.S.	M	52	42	25.8	16.8	1st	0.211	14.0	33.80	15.65	15.30	Quiet, breathing room air
						25.2	16.2	2nd	0.210	12.5	30.70	16.20	15.25	
		Mean			40.58	38.19	21.42		0.21	17.17	23.69	11.32	11.29	
		Twice S.E. of Mean			±1.75	±3.26	±1.42		±0.01	±1.73	±2.55	±1.01	±1.00	
		Range			(33-48)	(25.2-56.7)	(12.5-29.0)		(0.146-0.398)	(10.7-31.7)	(10.7-44.0)	(6.33-20.3)	(6.20-19.15)	

*The R values are expressed in scale divisions, 1 scale division = 4.55 mm. galvanometer deflection.

TABLE II. SUBJECTS WITH CONGENITAL HEART MALFORMATIONS

NO.	DATE	SUBJECT	SEX	AGE	HEMOGLOBIN (GM./100 ML.)	OXIMETER READINGS BEFORE INJECTION		PER CENT O_2 SATURATION	NUMBER	DYE INJECTED (MG./KG.)	INJECTION				DIAGNOSIS AND REMARKS
											MAXIMUM DEFLECTION (MM.)		MAXIMUM CONCENTRATION (MG./L.)		
						R SCALE*	IR (MM.)				RED CHANNEL	COMPUTER	CALCULATED	COMPUTED	
1	10/27/55	M.P. (Indian)	F	13 mo.	14.4	54.5 54.5	34.0 32.5	63.0	1st 2nd	0.190 0.190	10.1 5.9	7.4 4.8	4.83 3.52	4.90 3.78	Tetralogy of Fallot; quiet, breathing room air
2	11/ 4/55	N.R. (Negro)	F	7 yr.	12.8	28.6 27.2	21.8 20.8	63.0	1st 2nd	0.342	5.8 8.1	12.8 18.3	5.82 7.78	6.90 9.15	I.V.S.D. with normal pulmonary pressure; restless, breathing oxygen
3**	11/ 8/55	R.W.	M	16 yr.	17.3	14.3	10.1	72.5	2nd	0.416	23.7	80.0	31.70	33.30	Postop. tetralogy of Fallot; quiet, breathing room air
4	11/ 9/55	J.F.	M	6 mo.	15.8	55.0	34.0	76.0	2nd	0.415	10.9	8.7	5.02	5.40	Transposition of great vessels with overriding of pulmonary artery and initial stenosis; breathing room air
5	11/10/55	R.L.	F	7 wk.	11.0	71.0 65.0	38.0 36.0	96.0	1st 2nd	0.416 0.432	19.8 22.0	12.4 16.3	7.03 8.27	6.85 8.38	I.V.S.D. and I.A.S.D.; quiet, breathing oxygen
6	11/28/55	D.M.	F	5 yr.	10.3	45.5 42.8 41.0	26.5 26.5 26.8	96.3	1st 2nd 3rd	0.197 0.184 0.194	14.4 11.7 8.4	16.5 16.0 11.5	8.55 7.95 5.96	8.45 8.25 6.50	Constrictive pericarditis; quiet, breathing oxygen
7	12/ 6/55	T.C.	M	6 yr.	14.2	48.2	27.8	72.0	1st	——	5.8	6.0	4.08	4.27	Tetralogy of Fallot; quiet, breathing oxygen
8	12/ 7/55	G.P.	F	1 yr.	13.0	54.0 50.6 47.3	34.2 31.2 30.8	77.0	1st 2nd 3rd	—— —— ——	6.8 3.8 2.9	6.2 4.5 2.5	3.88 3.02 2.64	4.43 3.68 2.66	Undiagnosed cyanotic congenital heart lesion; breathing oxygen
9	1/30/56	L.McL.	M	12 yr.	12.6	38.7 35.0 33.9	19.9 19.2 18.0	87.0	1st 2nd 3rd	0.298 0.284 0.296	12.0 11.8 12.2	15.3 18.3 18.7	8.16 8.87 9.56	7.98 9.15 9.30	I.V.S.D. with pulmonary hypertension; quiet, breathing oxygen

10	2/13/56	D.L.	M	9 yr.	12.0	40.4 39.3 38.5	22.3 23.0 22.8	97.5	1st 2nd 3rd	0.196 0.198 0.192	19.3 16.8 15.3	29.6 26.0 23.0	12.65 12.54 11.75	13.58 12.15 11.00	Pure pulmonary stenosis; restless, breathing room air
11	3/22/56	S.M.	F	13 yr.	12.9	46.7 46.4 45.1	24.8 24.7 24.5	97.0	1st 2nd 3rd	0.416 0.435 0.438	16.7 20.8 19.7	16.0 22.7 19.5	8.02 9.65 9.34	8.25 10.88 9.63	Primary pulmonary hypertension; quiet, breathing oxygen
12	3/23/56	N.G.	M	2½ yr.	17.7	56.6 50.9	32.8 31.2	83.0	1st 2nd	0.420 0.408	6.7 17.0	3.5 15.9	3.05 6.15	3.23 7.65	Undiagnosed; sobbing, breathing room air
13	4/12/56	K.J.	F	14 mo.	10.3	63.7	34.8	96.5	1st	0.220	19.0	13.0	7.18	7.10	I.V.S.D. Eisenmenger type; quiet, breathing oxygen
14	4/19/56	B.S.	F	18 mo.	9.75	59.0 58.8	32.7 33.2	97.5	1st 2nd	0.301 0.394	10.0 12.9	6.9 9.6	4.78 5.90	4.70 5.75	I.V.S.D. with pulmonary hypertension; quiet, breathing oxygen
15	4/26/56	O.D.	M	14 yr.	11.6	38.8 38.8	23.2 23.2	94.0	1st 2nd	0.291 0.300	18.3 12.5	24.3 16.5	12.15 8.73	11.50 8.45	I.V.S.D.; quiet, breathing oxygen
16a	5/10/56	L.A.	F	10 yr.	10.4	48.6	27.2	98.5	1st	0.301	20.0	17.1	8.42	8.67	Preop. patent ductus arteriosus; quiet, breathing oxygen
16b	5/22/56	L.A.	F	10 yr.	12.1	48.5 46.1	27.5 26.8	96.0	2nd 3rd	0.308 0.330	16.0 16.1	14.7 16.1	8.00 8.90	7.75 8.30	Postop. patent ductus arteriosus; breathing oxygen
17	5/29/56	I.R.	F	11 yr.	13.3	39.3 39.3	21.8 21.8	95.8	1st 2nd	0.298 0.299	9.1 9.0	10.7 9.0	6.00 5.95	6.20 5.55	I.A.S.D.; quiet, breathing oxygen
18	9/21/56	S.F.	F	7 yr.	10.3	52.6 49.6	28.4 27.7	99.5	1st 2nd	0.346 0.444	12.8 20.7	9.7 19.0	6.10 9.80	5.80 9.40	I.A.S.D.; quiet, breathing oxygen
19	9/24/56	J.D.	M	10 yr.	14.4	34.6 33.8	20.5 19.8	88.0	1st 2nd	0.181 0.294	5.6 7.8	12.0 20.8	7.20 10.00	6.80 10.10	Undiagnosed (cardiac tumor?); quiet, breathing oxygen
	Mean				12.57	46.36	26.99	88.08		0.31	12.68	14.15	7.36	7.50	
	Twice S.E. of Mean				±0.94	±3.14	±1.71	±5.4		±0.03	±1.71	±2.05	±0.83	±0.81	
	Range			7 wk.-14 yr.	(9.75-17.7)	(27.2-71.0)	(18.0-38.0)	(63.0-99.5)		(0.181-0.438)	(2.9-22.0)	(2.5-29.6)	(2.64-12.65)	(2.66-13.58)	

*The R values are expressed in scale divisions, 1 scale division = 4.55 mm. galvanometer deflection.
**Not included in statistical treatment.
I.V.S.D. = interventricular septal defect; I.A.S.D. = interatrial septal defect.

was found to be about 0.5 mg. per liter plasma per millimeter deflection (1.94 and 2.1 mm. deflection in the normal and congenital groups, respectively). The slightly higher sensitivity recorded in the congenital group, consisting mainly of patients with intracardiac shunts, is due to the fact that the average values of the maximum dye concentration observed in this group was found to be significantly lower than that observed in the normal group and fall closer to the nonlinear portion of the calibration curve.

The deviation between the automatically computed and calculated values is slight, the standard deviation of the differences of all the determinations being 6.7 per cent, and in many instances it is difficult to decide which one of the methods is in error. The cumulative error in the values obtained by calculation based on the interpretation of individual instrument readings appear to outweight the inherent inaccuracy of the computer. In addition, apparently insignificant changes in the ear circulation during the recording which are automatically accounted for by the computer will escape all but the most careful scrutiny of the tracings.

The most serious difficulty, common to all methods based on the principle of oximetry and using T-1824 as indicator, is in obtaining a steady base line in patients with right-to-left shunts. In these cases it is necessary to administer oxygen to the patients in order to reduce the fluctuations in the background density of the ear due to changes in oxygen saturation; with careful management, satisfactory dye dilution curves can be obtained.

The instrument in its present phase of development is rugged in construction and its operation is relatively simple. However, the settings are somewhat critical in order to obtain the desired high degree of accuracy, and, therefore, have to be carried out by a trained person. It is of interest to note that since its completion about 2 years ago the instrument has required only slight readjustments and that the same earpiece with the original photocell is still being used. However, it was found advisable to change the light bulb twice during this period.

Attempts at the present time are being made to construct an earpiece which incorporates an interference filter in the red absorption band. It is hoped that by this means a linear relationship between the computer output and the dye concentration may be obtained, simplifying greatly the calibration of the instrument since only a few calibrating samples would then be required. In addition, the transfer of the recorded dye dilution curves directly to semilog paper, according to the method of Hamilton, will be easier.

SUMMARY

The principles of operation, methods of standardization and calibration of an instrument for recording the dye dilution curves and for the automatic quantitative estimation of the arterial concentration of T-1824 is described.

The sensitivity of the recording system appears to be adequate for recording several consecutive dye dilution curves when small quantities of dye, viz., 0.2 to 0.3 mg./Kg. per injection, are used.

Eighty-one comparisons were made between the dye concentration values computed automatically and those obtained by calculation. A close correlation between the results obtained by both methods in normal subjects and in patients with various cardiovascular anomalies was observed.

The results reported here, and others to be published separately in a paper on determination of cardiac output, indicate that the method described allows quantitative estimation of the dye concentration in the circulating arterial blood.

The construction and wiring of the instrument were carried out under the able direction of Mr. C. Pinsky, B.Sc., of the Department of Physiology, McGill University. We express our thanks to Mrs. C. Davis, B.Sc., and Mr. A. Stein, B.Sc., for their help in the reading of the tracings and in the preparation of the tables, and to Mr. G. Richard, B.Sc., for his assistance in the preparation of the drawings. Our thanks are due to Miss A. Pratt and Mrs. I. Cloutte for secretarial assistance.

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Ventricular Pre-Excitation (WPW) in the Presence of Bundle Branch Block

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There is a vast difference in the frequency of occurrence of bundle branch block and the pre-excitation syndrome in clinical electrocardiography. In a material of over 100,000 records the incidence of the former was found to be about 3 per cent, and of the latter, 0.08 per cent,[1] corresponding to a ratio of 40:1. Since the two conditions are attributable to two entirely different anatomic substrates (one usually acquired, the other probably congenital[2,3]) and, therefore, are independent, the statistical chance of their occurring together is about 0.24 per cent. In keeping with these figures, a search of the literature revealed only 5 instances[4-6] in which pre-excitation occurred intermittently in patients with bundle branch block. In all, the right bundle branch was the seat of the blocking lesion, and in at least 2 the presence of the latter was obscured by appearance of ventricular pre-excitation. None of the authors commented upon the implications of coexistence of the two different types of abnormal ventricular excitation.

This report is a result of a study of 3 cases in which this rare combination was diagnosed by us in routine electrocardiograms (12 leads). In 1 case pre-excitation is believed to have complicated a right-sided, and in the other 2 a left-sided, ventricular conduction defect located in one of the bundle branches. One of the cases was further complicated by a coexistent permanent depression of conductivity in ordinary A-V conduction pathways. The variety of observed electrocardiographic patterns provided an opportunity to analyze the circumstances which may permit or prevent simultaneous manifestation of bundle branch block and pre-excitation features in the scalar electrocardiogram.

MATERIAL

CASE 1.—A 67-year-old woman was admitted to the surgical service of Michael Reese Hospital for treatment of varicose veins. Her past history disclosed asthma for 20 years and attacks of palpitation for 5 years with sudden onset and termination. Examination revealed signs of emphysema and a diastolic gallop rhythm. The blood pressure was 130/70 mm. Hg.

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The electrocardiogram (Fig. 1) obtained as a routine procedure revealed sinus rhythm with a rate of 81 and QRS complexes of 0.16 sec. duration with features of both a right bundle branch block and ventricular pre-excitation. The bundle branch lesion is evident from widening and slurring of the terminal QRS portion, causing characteristically broad S waves in Leads I, aV_L, V_5, and V_6, and the notching at the top of the prominent R wave in V_1, V_2, and aV_R and at its downstroke in Leads III and aV_F. Characteristic pre-excitation features are represented by the slow rise or descent, respectively, of the inital QRS components, a delta wave, shortening the P-R interval to 0.12 sec. The upright direction of the delta wave in all leads (except aV_R) suggests simultaneous distribution of pre-excitation forces to both ventricles in dorsoventral direction. The abnormal configuration of the ST-T deflections in all precordial leads and in Leads II, III, and aV_F is attributable to secondary alterations of ventricular repolarization consequent to the two types of disorders of ventricular depolarization.

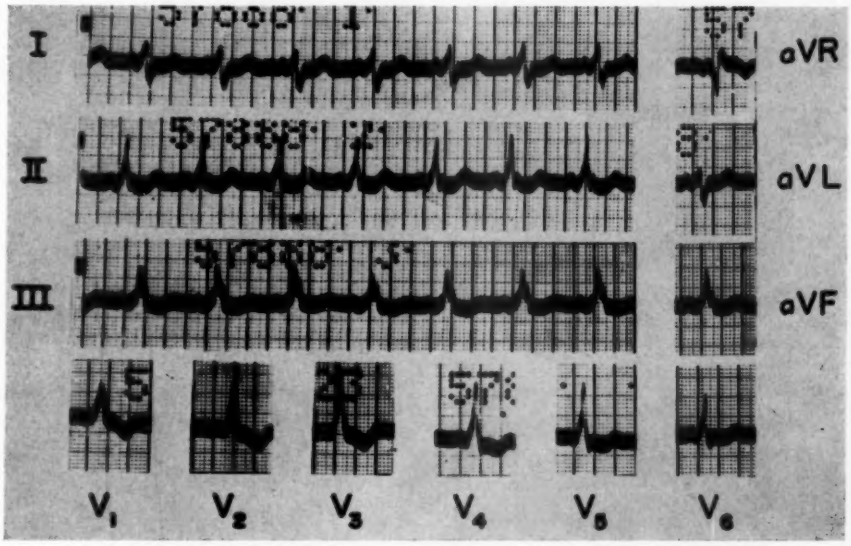


Fig. 1.—Case 1. Ventricular pre-excitation in the presence of right bundle branch block.

CASE 2.—A 22-year-old man was admitted to the medical services of the Michael Reese Hospital for a convulsive state. The history was that of an auto accident victim with trauma to the head 10 years ago. Cardiovascular findings were normal; the blood pressure was 140/80 mm. Hg.

The only electrocardiogram recorded (Fig. 2) reveals a sinus rhythm with a rate of 64 and prolongation of the QRS duration to 0.16 sec. The latter was attributed, on the basis of an analysis of the precordial leads, to ventricular pre-excitation in the presence of a left bundle branch block. Thus, in Leads V_1 to V_6 pre-excitation is strongly suggested by the association of an abnormally short P-R (0.10 sec.) with a heavily slurred initial component of QRS, a delta wave, accounting for the first 0.04 or 0.06 sec. of the entire QRS deflection. Its upright direction in these leads indicates simultaneous spread of the initial (pre-excitation) forces to both ventricles, this spread being in a dorsoventral direction. Thereafter the course of ventricular depolarization changes abruptly, proceeding in a right-to-left direction as indicated by the development of the deep S wave in the right precordial leads. Slow advancement of the activation wave toward the left ventricle, presumably via the ventricular septum, is suggested by the slurring and notching of the peak of the S wave in V_1 and V_2 and of the respective R wave in V_5 and V_6—all features characteristic of a left bundle branch block.

This dual cause for the abnormal QRS prolongation is not so clearly recognizable in the limb leads. Thus, in Lead I the initial prominent notch of 0.04 sec. duration could be considered to represent part of a P wave encroaching upon a smooth upstroke of R; in Lead III, on the other

hand, the P wave appears to be separated from QRS by a short isoelectric segment of corresponding (0.04 sec.) duration. However, if this were true then the QRS in these two leads would extend only over 0.12 sec.—a value corresponding to the duration in V_1 of the QRS portion occurring subsequent to the pre-excitation wave. These measurements compel the conclusion that (1) in Lead I the initial notch at the foot of QRS is the manifestation of ventricular pre-excitation rather than a P wave, the latter being isoelectric in this lead due to development of atrial depolarization in

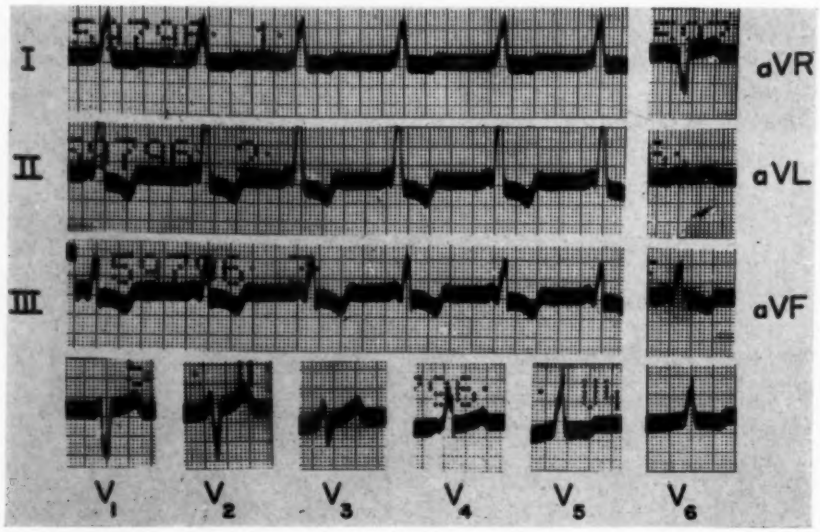
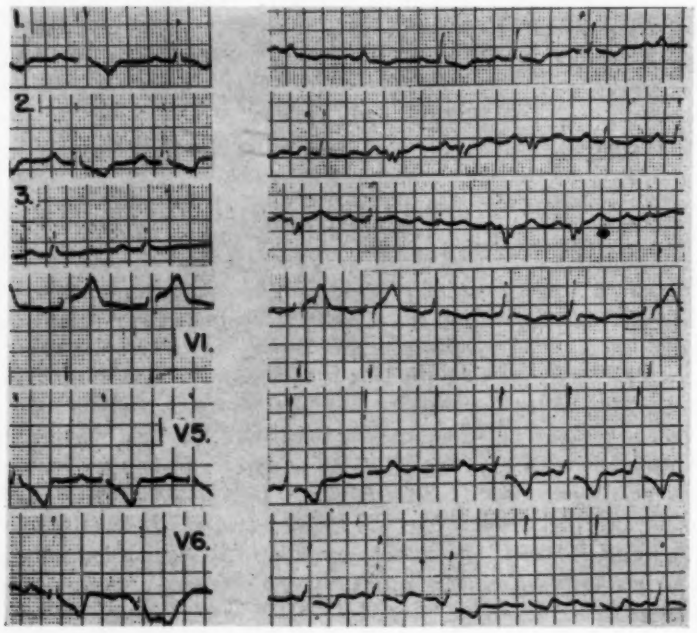


Fig. 2.—Case 2. Ventricular pre-excitation in the presence of left bundle branch block.



A. *B.*

Fig. 3.—Case 3. Intermittent ventricular pre-excitation in the presence of first degree A-V block and left heart strain.

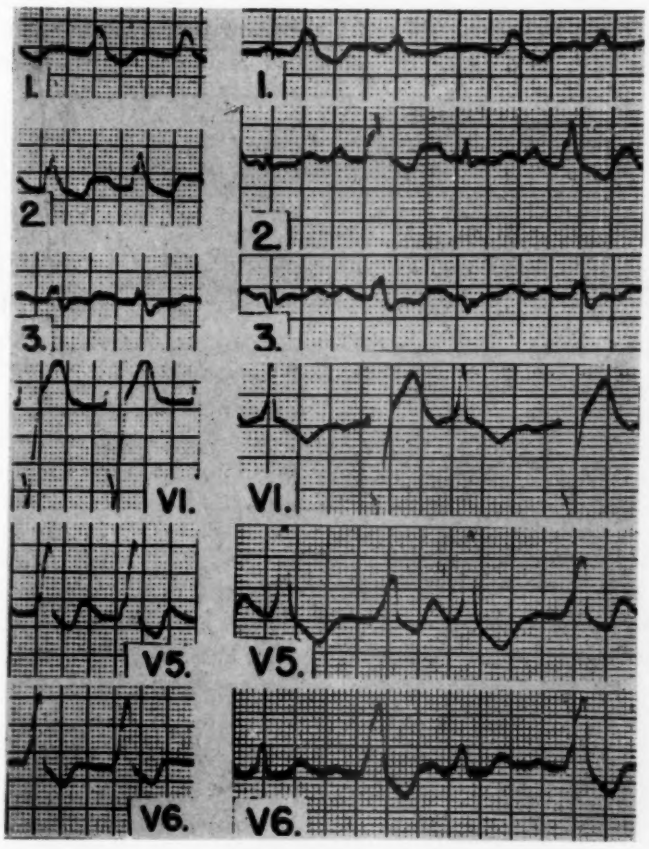
a direction perpendicular to Lead I, and (2) in Lead III the delta wave is isoelectric due to development of pre-excitation forces in a direction perpendicular to, and hence not manifested in, this lead. Corresponding considerations apply also to the interpretation of the other limb leads.

The ST-T deflections are discordant to the main QRS deflections in the leads in which the latter are large and entirely or predominantly upright or inverted—clearly a secondary change engendered by the abnormal course of depolarization. Leads V_1 and V_2, in which delta and T waves are upright in contrast to the main QRS deflection, suggest that the order of development of ventricular repolarization forces is dominated by the left bundle branch block rather than by the coexistent ventricular pre-excitation.

CASE 3.—A 56-year-old man was observed by the medical services of the Indianapolis Methodist Hospital for symptoms suggesting postural hypotension. The only abnormal finding on examination was cardiac enlargement thought to be due to arteriosclerotic heart disease.

A number of electrocardiograms was obtained on various dates and representative examples are shown in Figs. 3 to 5, in an order pertinent for the presentation. Record *A* of Fig. 3 (Oct. 10, 1955) shows a sinus rhythm (71) with a first degree A-V block (P-R of 0.24 sec.). The ventricular complexes are characteristic of left ventricular strain with a QRS duration of 0.10 sec. Normal direction of the initial ventricular activation is indicated by the small ("septal") Q wave in Leads V_5 and V_6. The P-S interval is 0.34 sec.

Record *B* (Dec. 3, 1955) of Fig. 3 reveals during sinus rhythm (rate 80) two types of ventricular complexes. One type resembles closely that seen in *A*, the resemblance being in regard to



A. *B.*

Fig. 4.—Case 3. Intermittent ventricular pre-excitation in the presence of first degree A-V and left bundle branch block.

contour as well as to P-R, QRS, and P-S values (0.24, 0.10, and 0.34 sec., respectively). The other QRS type is abnormally widened to 0.14 sec. by a delta wave that is upright in all precordial leads and best recognized in Leads V_5 and V_6, where it replaces the "septal" Q wave of the first type. Since with the appearance of these "anomalous" beats the P-R interval shortens to 0.16 sec. (and P-S to 0.32 sec.), intermittent ventricular pre-excitation in the face of a slight A-V conduction disturbance is strongly suggested. This interpretation is fortified by the occurrence of a series of such beats in which the P-R interval remains constant, and hence slight variations of the R-R interval are clearly attributable to concomitant variations of the P-P intervals. By the same token, an alternative interpretation, namely, intermittent ("isorhythmic") A-V dissociation due to acceleration of a ventricular pacemaker, can be ruled out. Simultaneous anomalous activation of both right and left ventricles by the sinus impulse is revealed by occurrence of upright delta waves over the entire precordium.

Record *A* in Fig. 4 (Dec. 13, 1955) shows during sinus rhythm (90) a typical pattern of a left bundle branch block with QRS prolongation to 0.14 sec. Partial superposition of P waves upon T waves precludes a precise measurement of the P-R interval which, however, is definitely prolonged, to at least 0.24 sec. as in Fig. 3,*A*.

Record *B* of Fig. 4 (Jan. 25, 1956) shows during sinus rhythm alternation of two types of ventricular complexes: one with a P-R of 0.24 sec. and a QRS duration of 0.16 sec. corresponding to the bundle branch complexes seen in *A*, the other with a shorter (not precisely measurable) P-R interval and QRS of 0.14 sec. duration corresponding to beats identified in Fig. 3,*B* as pre-excitation beats. Using the summit of P as initial point for measurement of the P-S interval, it is found to be 0.22 sec. in the pre-excitation complexes as against 0.32 sec. in the others.

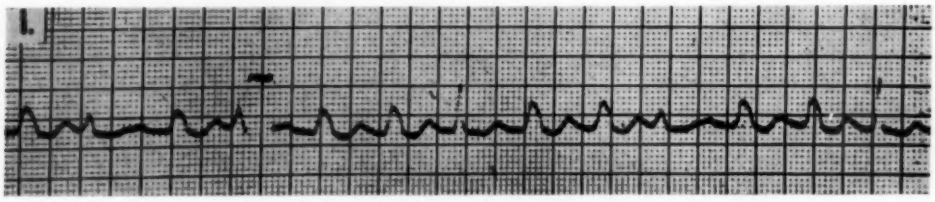


Fig. 5.—Case 3. Intermittent left bundle branch block and ventricular pre-excitation in the presence of first degree A-V block.

Fig. 5 shows Lead I of a record obtained on Dec. 6, 1955. During a sinus tachycardia of 125, the three types of ventricular complexes reproduced in Figs. 3 and 4 now occur side by side. Thus, in the first four beats bundle branch block alternates with pre-excitation, while in the rest of the tracing two bundle branch block complexes are followed alternately by a "normal" or a pre-excitation beat. Again the rapid rate, and consequent T-P superposition, prevents precise measurements of P-R and P-S intervals. When, as in Fig. 4, P-wave summits ("P") are used for the respective measurements, the values shown in Table I are obtained.

Comparison of these values reveals that the temporary block in the left bundle branch prolongs the QRS duration without altering the delayed A-V conduction, thereby prolonging the P-S

TABLE I.

	"P"-R	QRS	"P"-S
"Normal"	0.16	0.10	0.26
Bundle Branch Block	0.16	0.14	0.30
Pre-excitation	0.08	0.12	0.20

duration; on the other hand, during pre-excitation the pronounced shortening of A-V conduction time exceeds the increment in QRS duration, resulting in reduction of the P-S duration. Thus, the fundamental difference in the two abnormal mechanisms operating intermittently is clearly revealed.

COMMENT

The diagnosis of coexistence of ventricular pre-excitation with a ventricular conduction disorder was based on different criteria in each of the three cases. The recognition of the double disorder of activation of the two ventricles was simplest in Case 1 in which classical earmarks of both pre-excitation and a right bundle branch block were present. In Case 2 the diagnosis was strongly suggested by the appearance of the right precordial leads, in which a clear separation of the pre-excitation and bundle branch block forces was possible. Case 3 presented a special problem due to the lack of one of the features considered classical[7,8] for the diagnosis of the Wolff-Parkinson-White syndrome, namely, the short P-R interval. Nevertheless, the appearance in successive beats of a typical delta wave associated with a constant foreshortening of the prolonged P-R to a "normal" one, both in the presence and absence of a left bundle branch block pattern, can only be interpreted as intermittent ventricular pre-excitation. In the only instance of this kind reported,[3] the abnormal prolongation of the A-V conduction in the face of pre-excitation was ascribed to an anomalous A-V bypass originating within or below the A-V node, with concomitant depression of conduction through that portion of the node which was traversed by the undivided sinus impulse.

In all three instances the anomalous component was manifested as an upright deflection in all precordial leads, corresponding to a category designated as Type A by Rosenbaum and co-workers.[9] On this basis it would appear that the initial excitation wave took a dorsoventral direction and activation of both ventricles occurred simultaneously in a direction opposite to normal, that is, from the epicardial to the endocardial surface. Whether this premature depolarization started in a single, centrally located dorsal area and fanned out to the right and to the left, or in two or more regions simultaneously, is impossible to determine solely on the basis of the conventional precordial leads available for analysis. Initial dorsoventral spread of the excitation wave has been considered in instances of pre-excitation in which detailed study of the variations of the electrical field was performed with the help of extended precordial, esophageal, and intracardiac leads,[9,10] and in cases submitted to vectorial analysis.[11]

Ventricular depolarization, although initiated in similar fashion in all three instances, was then completed in each in a different manner. In Cases 1 and 2 the path of excitation was determined by the concomitant conduction disturbance in the right and left bundle branches, respectively—the terminal portions of the QRS complexes are typically those of right and left bundle branch block. This, of course, implies that large portions of the ventricular myocardium were not reached by the pre-excitation wave and remained accessible to that part of the sinus impulse which traveled down over ordinary A-V pathways and the unaffected bundle branch to the ventricles. The result was an unusual type of

ventricular fusion beats. Predominance of the "normal" over the anomalous component in this twofold type of ventricular activation is evident from: (1) the preservation of the typical earmarks of bundle branch block in V_6 of Case 1, and in V_1 of Case 2, indicating slow (trans-septal) spread of the impulse to the blocked ventricle, and (2) the direction of the repolarization wave in these leads, which is opposite to the bundle branch block component and hardly or not at all influenced by the direction of the pre-excitation wave.

The more complex situation in Case 3, resulting from the intermittent occurrence of both pre-excitation and a left bundle branch block, and further complicated by a concomitant first degree A-V block, can be unraveled on the basis of the comparative measurements summarized in Table I. The most outstanding fact in this respect is the foreshortening of the "P"-S interval of the pre-excitation beats when compared with the "normal" and bundle branch block complexes. This compels the conclusion that here, in contrast to Cases 1 and 2, ventricular depolarization was effected entirely by the pre-excitation impulse.[12] Transmission of the sinus impulse to the ventricles over ordinary channels and its participation in ventricular activation was prevented by the depression of conductivity in these fibers as manifested by the abnormally prolonged P-R interval in the absence of pre-excitation.

In keeping with this interpretation, comparison of the pre-excitation beats in Figs. 3 and 4 reveals almost identical features despite the presence of a bundle branch block on one occasion and its absence on the other. Hence, it would appear that had pre-excitation not ceased intermittently, the development of a severe left ventricular conduction disturbance could have been missed altogether. While it is a well-recognized fact that the altered sequence of ventricular activation inherent in the pre-excitation process may obscure abnormalities of the electrocardiogram caused by myocardial disease, especially myocardial infarction,[6] to our knowledge no note has been made as to the manner by which the electrocardiographic manifestations of a pre-existent conduction disorder may be altered by excitation of the ventricles via an accessory route[3] such as occurs in pre-excitation. We present our views as to the possible results of interplay of two or more such independent conduction disorders. As a background for our concepts, we utilized some of the established facts concerning the course of the ventricular activation in bundle branch block and pre-excitation, and the material which forms the basis of our report.

The original notion of Lewis that with interruption of conduction in one of the bundle branches, a uniformly slow excitation wave moves towards the blocked ventricle, has been confirmed experimentally,[13,14] although no agreement exists as to the exact location of the retardation. In the case of ventricular pre-excitation, on the other hand, agreement seems to prevail even among the protagonists of divergent theories[3] that ventricular activation starts prematurely in some parts of the myocardium remote from normal conduction fibers, in addition to activation of the two ventricles via the normal A-V conduction route. Analysis of the electrical field created by the anomalous component suggests that in some cases the premature depolarization starts in the posterior aspects of the ventricular surface, moving in dorsoventral direction toward both ventricles; in others

it has been found to have a predominant direction from right to left, corresponding to a right lateral origin of the pre-excitation wave. Both these varieties are consistent with the location of accessory muscle bridges, found in a few cases which were submitted to careful histologic studies.[15]

It becomes obvious from this study that electrocardiographic patterns resulting from the coexistence of pre-excitation and bundle branch block must be subject to considerable variations, depending on the seat of the bundle branch lesion, the location of the rapid A-V bypass, and the rate of impulse conduction through the ordinary normal A-V junction.

1. Assuming that pre-excitation and a bundle branch block are *homolateral* and that A-V conductivity is unimpaired, then the pre-excitation can be expected to dominate the blocked ventricle, replacing the trans-septal activation front advancing from the unblocked ventricle. These two waves may interfere with each other and result in a ventricular fusion beat. Should, however, conductivity in the A-V junction be depressed, pre-excitation will proceed without interference from the blocked to the unblocked ventricle, thus activating both ventricles, as in Case 3 of this report (Figs. 3-5).

2. Supposing, on the other hand, that pre-excitation and bundle branch block are completely or partly *contralateral*, then the side with the uninterrupted bundle will become activated rapidly by two competing wave fronts, one using accessory and the other ordinary A-V channels. Activation of the other ventricle, however, will be completed with considerable delay. If this ventricle is not reached by the pre-excitation process, as in the case of a laterally located A-V bypass, its depolarization will depend entirely on the trans-septal impulse spread from the other ventricle. On the other hand, in the presence of a posterior A-V bypass, its activation will start prematurely but will be completed with delay, since both the pre-excitation and trans-septal impulse travel over ventricular fibers with a slow conduction rate. In both instances the earmarks of pre-excitation as well as of bundle branch block will be preserved in the electrocardiogram—as exemplified by Cases 1 and 2 (Figs. 1 and 2) of this report.

CONCLUSIONS

1. Pre-excitation may coexist with either a right or left bundle branch block.

2. The recognition in the electrocardiogram of the twofold disorder of ventricular activation is possible if pre-excitation takes place in the chamber with the uninterrupted bundle.

3. Pre-excitation may obscure the electrocardiographic pattern of a bundle branch block if the chamber with the interrupted bundle is activated prematurely.

4. When pre-excitation starts simultaneously in both ventricles, earmarks of bundle branch block may be obscured by depression of conduction in the normal A-V pathways.

SUMMARY

1. Three cases are reported manifesting the rare combination of ventricular

pre-excitation with a right or left bundle branch block. This was recognized in routine 12-lead electrocardiograms.

2. In one instance the presence of a first degree A-V block did not preclude the diagnosis of ventricular pre-excitation but could be established as the factor responsible for masking the features of a left bundle branch block.

3. The variety of electrocardiographic manifestations which may result from the combination of these two types of abnormal ventricular activation are discussed in the light of present knowledge concerning impulse propagation under normal and anomalous circumstances.

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Electrical Alternans: Case Report and Comments on the Literature

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Electrical alternation of the ventricular complexes in the experimental animal was first reported by Hering.[1] In 1910, Lewis[2] first reported its occurrence in a patient with auricular paroxysmal tachycardia. Reviews of further cases in man have been made by Laubry and Poumailloux,[3] Kalter and Grishman,[4] Kalter and Schwartz,[5] and McGregor and Baskind.[6] Additional single cases have been reported by Kisch,[7] Hellerstein and Liebow,[8] and Arya,[9] to make a total of 64 published examples. Forty-nine of these had sinus rhythm, 11 had paroxysmal tachycardia, and 4 auricular fibrillation or flutter. One human case of isolated alternation of the P wave has been recorded.[10]

It is the purpose of this paper to describe a case in which electrical alternans of the QRS complexes was associated with alternation in the intensity of the first heart sound, and with transient alternation of the P wave. Pulsus alternans was consistently absent. Comments are made on the pathologic significance and mechanism.

CASE REPORT

Mrs. M., at the age of 54 years, underwent right mastectomy. Hypertension (blood pressure = 220/130 mm. Hg) was then the sole cardiovascular abnormality, and x-ray showed a normal cardiac shadow. A year later, when local metastases were excised from the right axilla, the patient admitted to slight exertional dyspnea of several months' duration. Apart from hypertension (blood pressure = 220/110 mm. Hg) the cardiovascular system was clinically normal. X-ray now showed an enlarged heart of hypertensive contour, and shadows of metastases in the right upper zone and at the right hilum.

Three months later the patient was admitted to Maryfield Hospital under the care of Professor I. G. W. Hill. Her dyspnea had become progressively worse over the previous 6 weeks and she had developed congestive cardiac failure with orthopnea, cyanosis, and moderate edema of the lumbosacral region and legs. The jugular veins were overfilled and pulsated freely. The pulse was 100 per minute and regular. The heart was moderately enlarged to the left. On auscultation there was a striking alternation in the intensity of the first heart sound at and internal to the apex. Blood pressure was 180/110 mm. Hg. Despite repeated careful palpation of the pulse, and sphygmomanometry, no pulsus alternans was detected. There were signs of a right pleural effusion. X-ray confirmed this, in addition to showing the previous abnormalities.

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An ECG, sections of which are shown in Fig. 1, showed alternation in the amplitude or form of the QRS complexes in standard and unipolar limb leads, and in Leads $V_{1,3-6}$. In V_2 less regular and minor fluctuations in voltage were present. There was no direct relationship between the electrical alternans and respiration. Among many ECG recordings, associated alternation of the P wave and QRS complex was noted once (in Lead V_1).

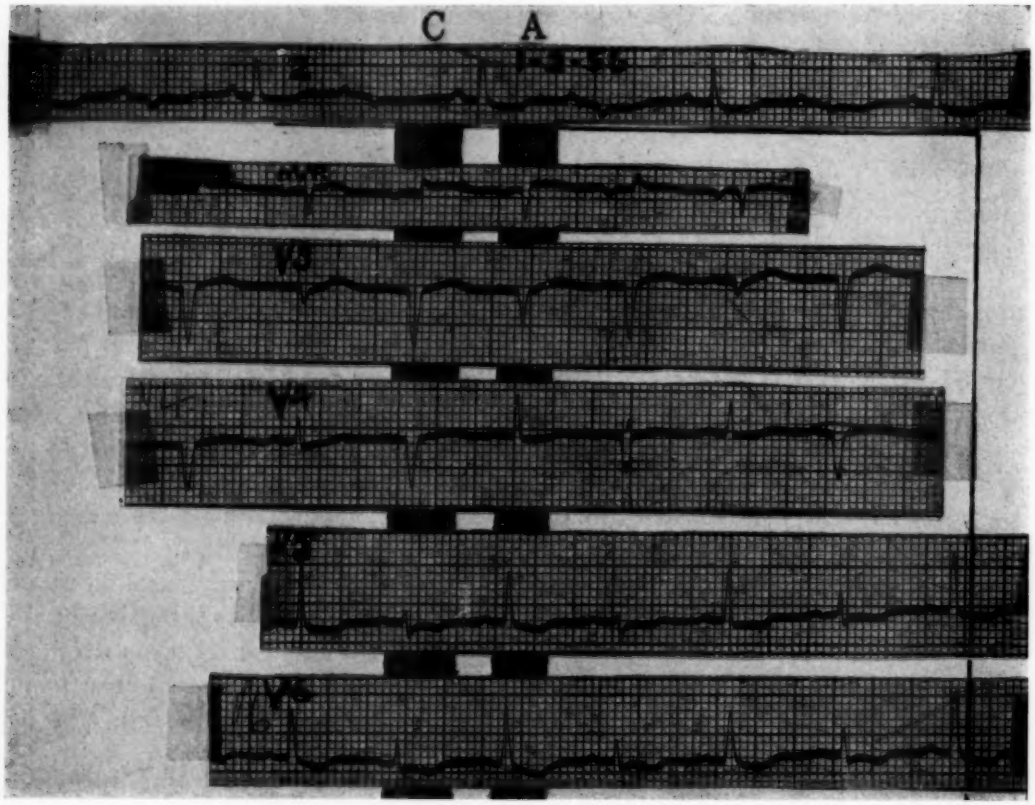

Fig. 1.—Electrical alternans of QRS complexes. Those in Column C are considered to have been recorded during clockwise rotation, and those in Column A during anticlockwise rotation. See text.

Temporary clinical improvement followed the administration of digitalis and mercurial diuretics, but after 1 month in hospital the patient had become extremely weak. Blood pressure had fallen steadily and on the day before her death was 130/80 mm. Hg. For the last 3 days of life, when her cardiac failure was again increasing, the alternation in the intensity of the first heart sound was imperceptible, and the ECG showed no electrical alternans.

Abstract of Autopsy Report (*Dr. H. McD. Cameron*).—The pericardium was distended by a large bloodstained effusion. The heart weighed 300 grams. The epicardium was extensively infiltrated by carcinoma, which, partly encasing the heart, was thickest over the anterior surface of the ventricles. The lateral aspect of the left ventricle was relatively free of growth (Fig. 2). The chambers and valves were macroscopically normal.

Small spherical metastases were present in both lungs. A large area of the right lung base was diffusely infiltrated, and a large sanguineous effusion was present in the right pleural cavity. Secondary deposits were present in the liver and both adrenal glands.

Histology showed the epicardium to be thickly infiltrated with adenocarcinoma similar to the primary mammary carcinoma originally removed. Invasion of the myocardium was mostly confined to small bands extending along the intermuscular septa or lying in veins. In a few areas penetration into the myocardium was deep, and in one block of the interventricular septum there was diffuse infiltration by numerous small islands of growth. In the right ventricle a subendocardial deposit was situated on the margin of one of the trabeculae carneae.

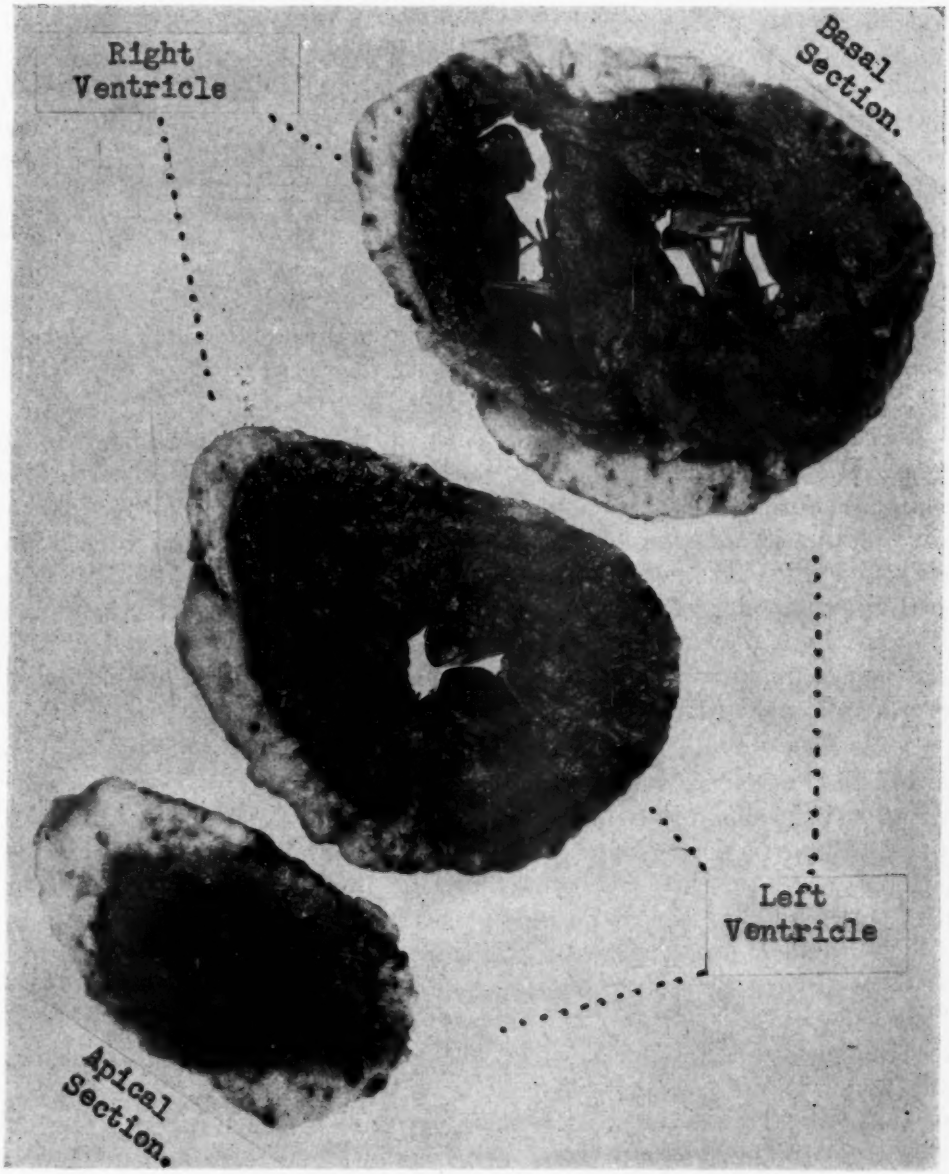

Fig. 2.—Cross sections of the heart to show the general distribution and extent of malignant tissue. Note the relatively slight involvement of the posterolateral wall of left ventricle in the upper two sections.

DISCUSSION

Assessment of the significance of this example of electrical alternans involves consideration of the relevance of the associated pathology and of the underlying mechanism.

Pathologic Significance.—It is well known that heart disease is usually absent in those cases of electrical alternans with paroxysmal tachycardia, in contrast to the almost invariable presence of cardiovascular abnormalities in those cases with sinus rhythm.* The heterogeneous nature of these abnormalities has been emphasized previously.[4,5] Although no specific pathologic significance can be attached either to alternation of the QRS complex alone or to concomitant alternation of QRS complex and ST-T segment, associated alternation of auricular and ventricular complexes was noted by McGregor and Baskind[6] to be present only in cases with pericardial effusion.

The present case is a further instance of such associated auricular and ventricular alternation in the presence of pericardial effusion, although alternans of the P wave was only transient. It is therefore probable that of the three obvious cardiovascular abnormalities (hypertension, myocardial metastases, and pericardial effusion) the last condition was the factor responsible for the electrical alternans.

Mechanism.—Alternate change in cardiac position was postulated by McGregor and Baskind[6] as the likeliest cause of QRS alternation occurring with pericardial effusion, since such a mechanism could account for concomitant P-wave alternation in some of these cases, and for the associated alternation in heart sound intensity (not due to pulsus alternans) in one of their own cases. These authors considered that pericardial effusion, by increasing cardiac mobility, could sometimes allow a natural period of oscillation capable of responding in a 2:1 fashion to the heart beat. At other times a less regular oscillation might give rise to irregular fluctuations in voltage in the ECG.

In the case here described, the associated, though transient, P-wave alternation and the "auscultatory alternans" might be likewise regarded as indicating alternation in cardiac position, this mechanism also accounting for the QRS alternans. But it is suggested that further evidence of positional changes, of a rotational nature in this case, is provided by the QRS patterns in Lead aV_R and in the precordial leads. The complexes in Columns C and A in Fig. 1 are considered to have been recorded with the heart rotated clockwise and anticlockwise, respectively. Such a mechanism could account for the qr and QS complexes in Lead aV_R, and for the fact that V_4 shows QS waves like those in V_3, alternating with complexes consisting of R waves like those in V_5. The marked change in configuration of successive QRS complexes in V_4 suggests that this lead recorded potentials from a transitional zone, the abruptness of which may have been determined by the fairly sharp line of demarcation between malignant tissue and relatively healthy myocardium (Fig. 2).

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*Electrical alternans with sinus rhythm in a normal heart has been reported in only one patient.[7] As the heart rate in this infant was 170/min., the significance of the electrical alternans might be considered as similar to that in paroxysmal tachycardia.

The occasional slight dissimilarities in the small (or large) complexes in the same lead, as in the second and sixth complexes in V_5 (Fig. 1), are compatible with varying degrees of rotational movement. The disappearance of the electrical alternans in the final ECG, which showed evidence of marked clockwise rotation, may have been due to a change in the natural period of cardiac oscillation because of increased intrapericardial tension, or to a change in heart rate which in this ECG varied between 83 and 107 per minute, whereas the rate in those tracings showing electrical alternans ranged from 100 to 115 per minute.

Thus, the present case supports the hypothesis of McGregor and Baskind[6] that QRS alternans, when associated with pericardial effusion, is due to alternation in cardiac position. These authors postulated such a mechanism only for cases with pericardial effusion. But if the interpretation of alternate rotational changes, based on the precordial QRS patterns as described in this case, is valid, then on the same basis a similar mechanism is suggested as a possible cause of the electrical alternans, in the absence of pericardial effusion, in a case reported by Hellerstein and Liebow.[8] It is, however, not possible by such analysis of the precordial electrocardiograms to determine the incidence of this mechanism, since most cases of electrical alternans were reported before the general use of multiple precordial leads.

SUMMARY

A case of electrical alternans of the QRS complex associated with alternation in the intensity of the first heart sound is described. Transient concomitant P-wave alternation was noted.

Autopsy showed malignant invasion of the myocardium and pericardial effusion.

The pathologic significance and the possible mechanism of the electrical alternans are discussed. It is concluded that the relevant pathologic factor was the pericardial effusion, and that the mechanism was one of alternation in cardiac position. It is suggested that such a mechanism may not be confined to cases with pericardial effusion.

I am grateful to Professor I. G. W. Hill for his advice and criticism, to Dr. H. McD. Cameron for the pathology report, and to the staff of the ECG Department for their assistance.

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Diverticulum of the Left Ventricle: Case Report With Special Reference to Electrocardiographic Findings

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The subject of diverticulum of the left ventricle of the heart was reviewed, in 1951, by Skapinker,[1] who also reported the successful removal of a diverticulum in an infant. Of the 13 cases he found in the literature, only one survived infancy without surgical resection, and this one died as a result of rupture of the diverticulum at the age of 4 years. Since then, Parsons,[2] in addition to describing a case of ventricular extension into the abdominal wall in an infant, has drawn attention to a similar case previously mentioned by him, and to cases described by Formijne[3] and Snellen and associates.[4] In all these latter cases evidence of associated congenital cardiac abnormalities was present. The following is the report of a ventricular diverticulum in a young adult without disability or other discernible congenital defects in the cardiovascular system.

CASE REPORT

A male Bantu, aged 17 years, came to Durban to seek work. On registering for employment he was seen by the medical officer and referred to hospital for investigation. He was symptom-free but had had a swelling in the upper abdomen for as long as he could remember. This had slowly enlarged as he grew older. Confirming this history, his mother said that the swelling was present at birth and had increased steadily in size.

On examination there was a swelling in the epigastric region 2 inches above the umbilicus (Fig. 1). It was 1 inch wide by 2.5 inches long, somewhat pear-shaped and hanging vertically downward. A large tortuous, pulsating vessel passed down from beneath the xiphisternum to become continuous with the base of the swelling, while the base of the tumor was attached to the umbilicus by a nonpulsating cordlike structure. The swelling appeared to be just under, but not attached to, the skin. There was marked systolic expansile pulsation. However, when the superior feeding vessel was obliterated by manual compression, the tumor became smaller, and slight, independent systolic contraction could be seen. On compressing the tumor itself, premature beats occurred both in the mass and the heart. Systolic and diastolic thrills could be felt over the feeding vessel and tumor. A soft diastolic murmur was present at the cardiac apex, and, as this was traced down to the feeding vessel, it became progressively louder and rougher, and to it became added a loud, rough systolic murmur.

The rest of the cardiovascular system was normal. The apex beat was in the fifth left intercostal space 3 inches from the midline. The heart sounds at the base were normal and closed.

From the Department of Medicine, University of Natal, Durban, South Africa.
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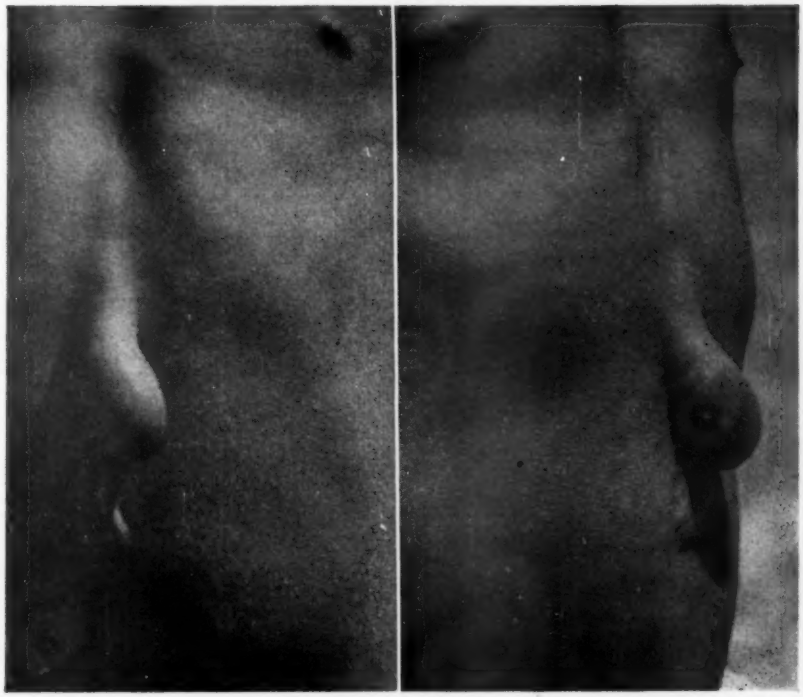

Fig. 1.—The patient with diverticulum protruding in epigastric region.

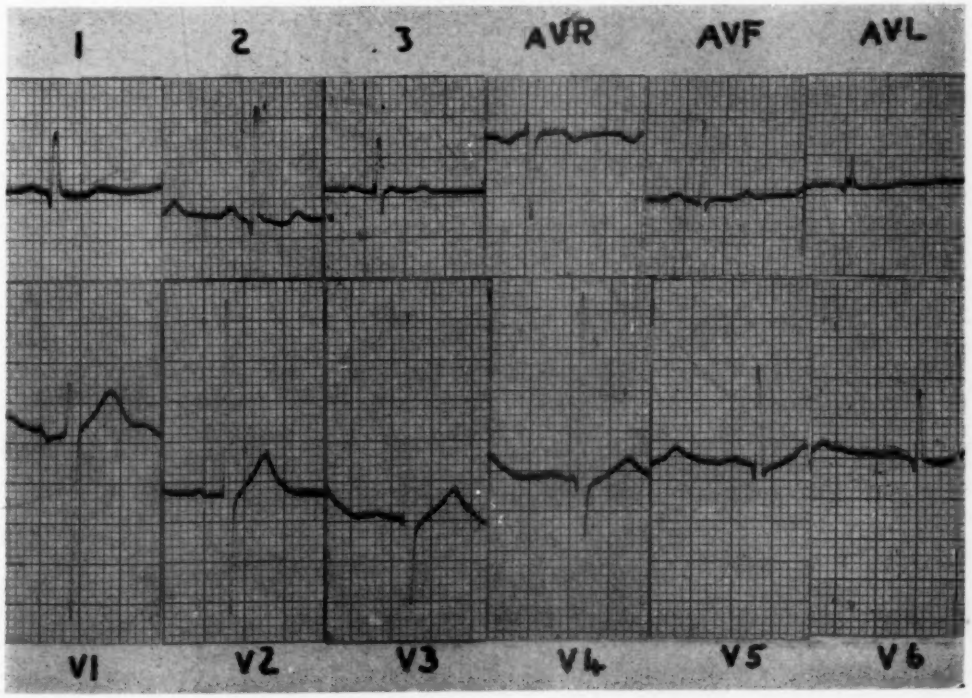

Fig. 2.—Standard electrocardiogram showing no abnormality.

The pulse rate was 86 per minute. It was regular and not collapsing. The blood pressure was: left arm 115/70 mm. Hg, right arm 95/70 mm. Hg, left leg 120/75 mm. Hg, and right leg 130/85 mm. Hg. Physical development was average, and no abnormality was found in any other system.

Radiologic Investigations.—Straight x-ray and screening of the heart showed that the heart was not enlarged, but there was a prominent, vigorously pulsatile pulmonary outflow tract. A soft tissue swelling could be seen overlying the abdomen.

Angiography: At first a polythene catheter was passed down into the channel connected to the pouch, and 50 c.c. of 70 per cent diodone was injected. This demonstrated the sac, and

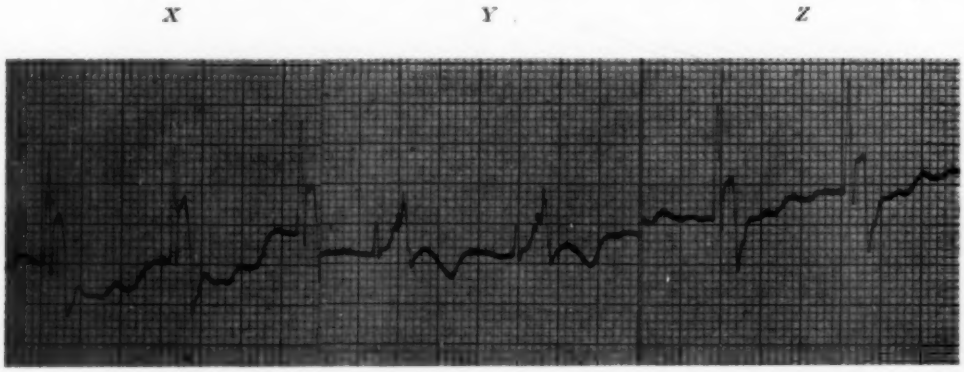

Fig. 3.—*X* and *Z* electrode on either side, adjacent to mass. *Y* electrode on mass. Double QRS complexes present.

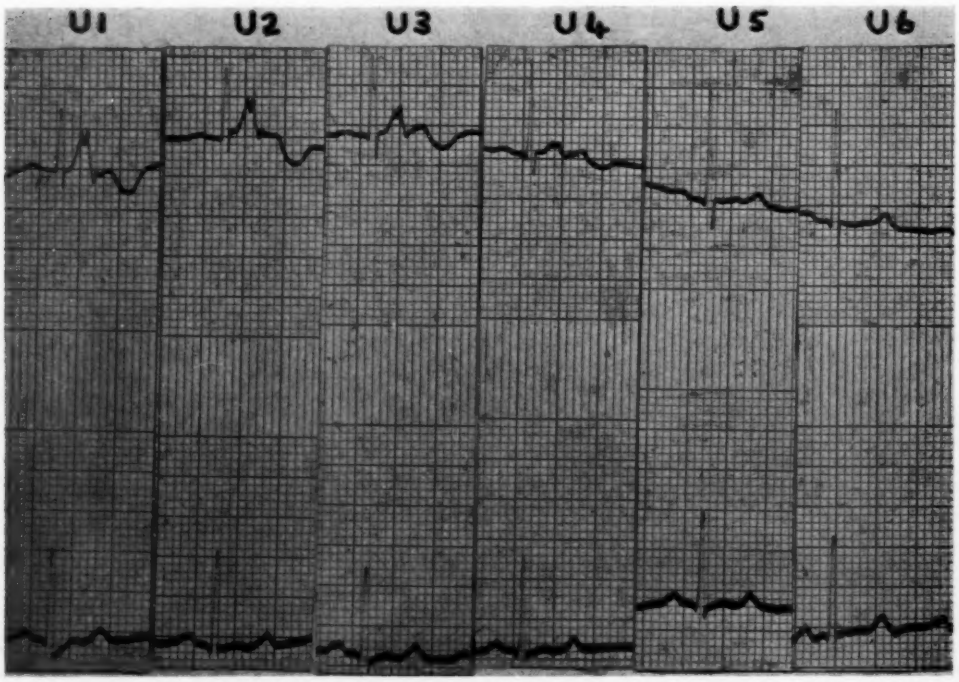

Fig. 4.—Two-channel electrocardiogram consisting of Lead II and unipolar Leads U1-U6 taken successively in a line from a point adjacent to the mass to the cardiac apex. These show a double QRS complex in U1 which gradually diminishes in amplitude until it is absent in U6.

a vertical channel above it, apparently with a double lumen, some 12 cm. long. A further angiogram was performed with the catheter passed upward in the channel connected to the pouch, and 60 c.c. of 70 per cent diodone was injected. The catheter passed into the left ventricle, and the left ventricle, aorta and its branches were outlined. The channel appeared to enter the left ventricle at, or near, its apex.

Although surgery was advised, the patient refused to remain in hospital, and returned to his home in the country. He has not attended for follow-up.

DISCUSSION AND ELECTROCARDIOGRAPHIC FINDINGS

An electrocardiogram using the standard and routine chest leads showed no abnormality, but with leads taken adjacent to and directly over the mass a double QRS complex was seen (Figs. 2 and 3).

A two-channel electrocardiogram using Lead II in one channel, and a unipolar lead placed at 6 sites (U1—U6) taken successively in a line leading from the mass to the cardiac apex showed the following: (1) The initial complex corresponded in timing, in expected contour, and in elevation with the normal

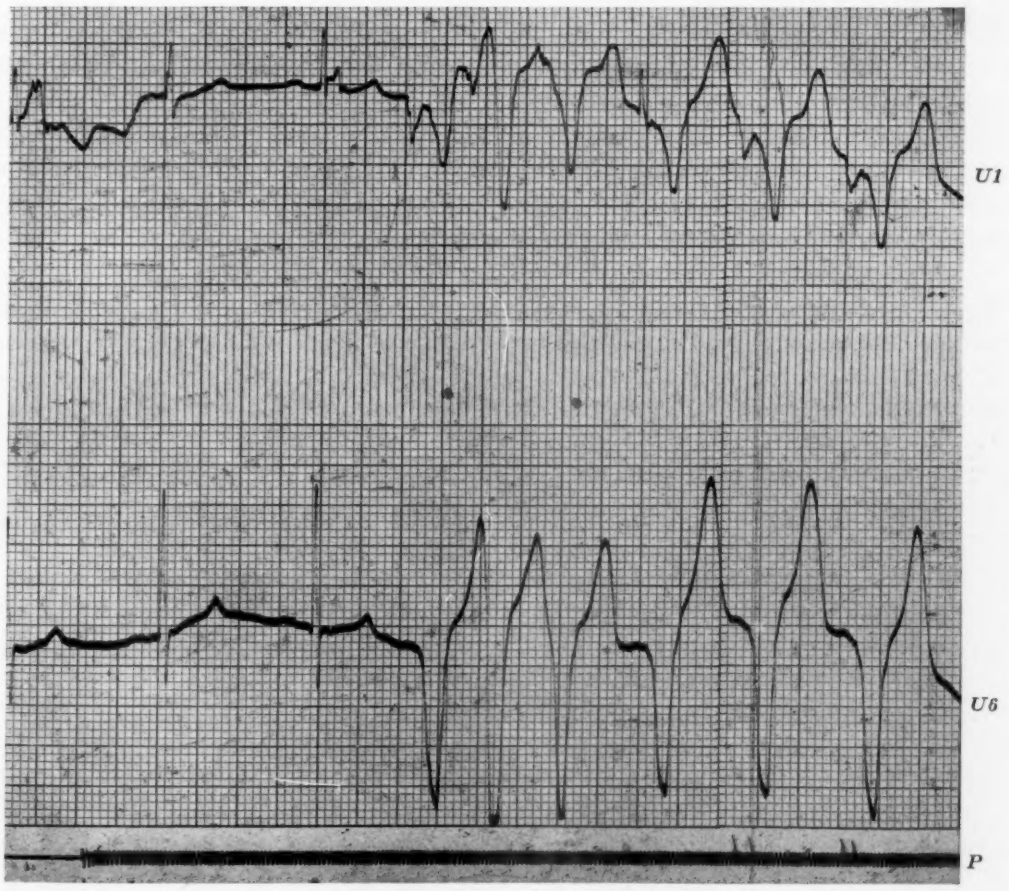

Fig. 5.—Two-channel electrocardiogram with pressure applied to mass. The premature beats show double, retrograde QRS complexes in U1, and single, retrograde complexes occurring at least 0.08 second later in U6. (P = pressure.)

cardiac QRS. (2) It was followed immediately by a broadened and notched QRS complex ending at least 0.12 second after the normal QRS. An inverted T wave followed. (3) As the leads progressed further from the mass toward the cardiac apex there was a gradual diminution in amplitude of the additional QRS until it was completely absent in U6 (Fig. 4).

The electrocardiographic findings indicated the presence of actively depolarizing and repolarizing muscle in the tumor wall.

A continuous electrocardiographic strip taken with premature systoles being produced by compressing the tumor revealed the following (Fig. 5):

In Lead U1 double retrograde QRS complexes were seen, while the corresponding complexes in U6 were single and retrograde. The onset in U1 was at least 0.08 second earlier than the apparent onset in U6 (which was sufficiently remote from the tumor not to pick up its potential). This apparent delay could be explained only by assuming that an ectopic focus in the tumor stimulated the heart muscle by retrograde spread of the depolarization wave from the tumor via a connecting cardiac muscular channel to the heart muscle, the apparent delay representing the time taken for the wave to spread from the tumor up to the heart. This clearly indicated that the muscle in the tumor was part of the normal cardiac syncytial mass.

SUMMARY

1. A case of diverticulum of the left ventricle of the heart in a male Bantu, aged 17 years, is described.

2. The electrocardiographic findings are discussed. These clearly show the presence of an ectopic focus in the tumor, capable of initiating impulses and conducting them to the heart via a connecting cardiac muscular channel. This finding was of considerable value in diagnosis.

Thanks are due to Dr. A. J. Wilmot for allowing me to study this patient who was under his care, to Dr. S. Disler, Medical Superintendent, King Edward VIII Hospital, for permission to publish this case, and to Dr. L. Norris for his help with the two-channel electrocardiograms.

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A Clinical Comparison of Three VCG Lead Systems Using Resistance-Combining Networks

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The design of lead systems which use resistance-combining networks to compensate for irregularities of the body constitutes an important advance in vectorcardiography.[5,6,10] Previously, the vectorial loops obtained with various electrode placements differed so widely that comparisons between clinical series were virtually useless.[3,8] With correcting networks, it becomes possible (according to the dipole theory) to obtain similar tracings from an infinite variety of electrode positions.

Lead-system networks can combine the signals derived from various electrodes on the body to give approximately orthogonal components of the heart vector.[2] Homogeneous torso models, in which current dipoles replace the heart, have been used to obtain the data required for the design of these circuits. Although such data may be approximately correct, they will not apply with equal accuracy to patients with different bodily configurations or heart positions. It is possible to reduce the error, in cases in which the heart's position does not correspond to that of the dipole in the model, by making the effects of individual variation of the position of the heart cancel themselves. This is achieved by the use of extra electrodes strategically placed so that heart vectors originating anywhere within a relatively large region are equally represented.[5,10] Since the resultant heart vector represents the sum of countless small vectors distributed (for all we know) anywhere in the region occupied by the heart, a lead system that can represent all these with equal weight can give a true average of the heart vectors. Such a system may be called a vector-averaging system.

Although it is clearly an advantage to have a lead system that will not neglect some regions of the heart, or accentuate others, and that will not be affected by individual variations of the heart's position, clinical use imposes a severe restriction on the number of electrode positions that may be theoretically desirable to achieve such a result. The minimum number of electrode positions for spatial

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vectorcardiography is, of course, four.[5] Of the two vector-averaging systems currently proposed, one uses seven[5] electrodes and the other uses fourteen.[10]

The 7-electrode, vector-averaging system was introduced by Frank,[5] as being both clinically practical and accurate. Although the 7-electrode system is probably an excellent compromise between accuracy and convenience for patients who can sit up and sit still, the time required for its application (according to Frank, 15 to 20 minutes) and the degree of patient disturbance involved tend to preclude its use in very sick patients. In addition to requiring the application of a rather large number of electrodes, two of which must be placed at the back of the patient, the 7-electrode system has the disadvantage that one of the electrodes (C) requires the use of a chest protractor.[5] The latter is necessary because the signals that this electrode picks up are very sensitive to positional change (lying, as it does, near the transitional zone of the ECG), and also because there is no convenient landmark that can be used to fix it. It seems likely that full acceptance of the VCG as a clinical tool, applicable not only to patients who are unworried and cooperative but also to those who are distressed and sick, will be delayed until the degree of patient disturbance can be made to approach that pertaining to the ECG.

Practical advantages in using a simpler system led Frank and Seiden[6] to consider a 4-electrode system which used the electrode positions employed in the tetrahedral system of Wilson and associates.[11] The data needed in the calculation of the resistance-combining network of the 4-electrode system were obtained from the same torso model as that used for the 7-electrode system.[6] This 4-electrode system and network will be called the RLFB in this paper. In an extensive comparison of these two systems, these workers found that, although the agreement was good in some patients, it was poor in others. This variation in agreement was thought to be due to a greater sensitivity of the RLFB to variations in the heart's position. The results of the comparison led to the rejection of the RLFB for clinical use in favor of the 7-electrode system.

To date, no lead system has been proposed in which electrode sites were chosen primarily on the basis of convenience. Before the introduction of combining networks, electrode positions were chosen in the hope that the lead axes would be orthogonal.[1,7,9] There was also the desire (of some) to shun precordial sites, in the belief that these would be unduly sensitive to immediately subjacent effects. Such considerations guided Wilson and associates in their choice of electrode sites in the tetrahedral system.[11] Frank has removed these considerations: as well as designing networks to achieve lead axis orthogonality, he has shown that earlier objections to the use of precordial sites were largely unfounded.[4] Nevertheless, Frank and Seiden chose for their 4-electrode alternative to the 7-electrode system the very sites used in the Wilson tetrahedral system. Although these sites had the merit of familiarity, the use of a back electrode was unfortunate because it gave sagittal signals which were both small and distorted.[6] Nor was the back the most convenient site for a sagittal lead, especially in ill patients.

The present investigation was undertaken in the hope that suitable resistance-combining networks and the use of precordial sites might lead to an acceptable 4-electrode system for clinical application.

METHODS AND MATERIALS

For the 4-electrode system chosen in this study, the following electrode sites were selected: the right arm, R; the left mid-axillary line at the level of the fifth intercostal spaces at the sternum, A; the left leg, F; and the anterior median line, E, at the same level as A (Fig. 1).* Self-retaining suction electrodes were used for the A and E positions. It was decided to follow Frank's suggestion that the left arm should not be used.[5] Instead, the A-position was chosen because (1) it was hardly less convenient, (2) it gave bigger signals, and (3) it avoided errors arising out of the mobility of the left arm in a region of steep electrical gradient.†

The signals derived from the 4 electrodes were delivered through cathode-followers to the network of resistors shown in Fig. 1. A separate ground electrode was not required because the

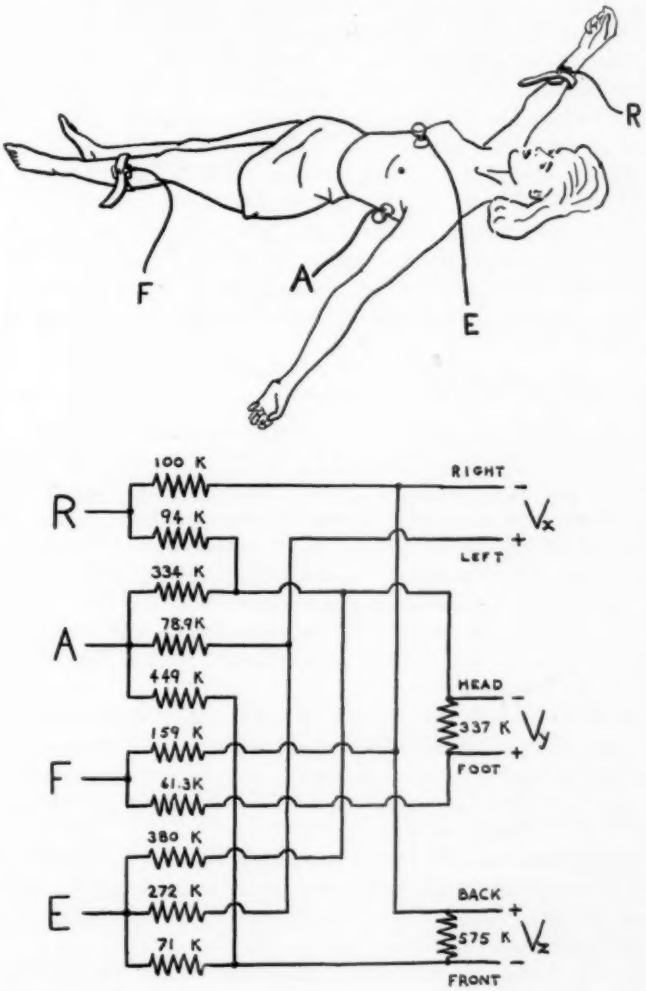

Fig. 1.—Electrode positions (above) and combining network (below) for the RAFE 4-electrode system.

*Positions A and E correspond to similarly named positions in the 7-electrode system.

†A further advantage in this choice of the A-position, rather than the left arm, is that the 4 electrodes embrace the origin of image space and can be used, therefore, with the appropriate network, to give a "central terminal," the accuracy of which will depend upon the accuracy of the image-surafce data used in the calculation of the network.

ground lead could be attached to any of the R, A, F, or E electrodes. The resistance network was calculated from image-surface data published by Frank.[2,5] The coordinates of the electrode positions in image space were taken to be as follows: R (−50, −60, 20); A (95, 0, 58); F (−21, 95, 9); and E (−60, 0, −130). These apply to the same image surface as that used in the determination of the networks for the 7-electrode and RLFB systems.[6] This 4-electrode system and network will be termed the RAFE.

The 7-electrode system, the RAFE, and the RLFB were compared in this study. Frank and Seiden carried out their RLFB-7-electrode system comparison under what might be termed laboratory conditions, in that most of the patients were sitting (those who were not sitting were prone) and an electrical procedure was used to determine the level of the electrical center of the ventricles.[6] Because the RAFE was intended for use under clinical conditions, on sick patients, it was decided to make this comparative study with the patients supine, and the level of the electrical center of the ventricles was taken to be that of the sternal ends of the fifth intercostal spaces, as recommended by Frank.[5] The RLFB was included because it was felt that larger differences between it and the 7-electrode system might be encountered under these circumstances.

The signal amplitude level of the RAFE is set by the X-component (it being less than the Y- or Z-components), which has a magnitude of 99 units. Because this is fairly close to the minimum image vector of the 7-electrode system, which has a magnitude of 136 units (for the Y-component), no change in amplification was required when changing from the 7-electrode system to the RAFE (amplitude ratio of 0.73). For the RLFB, however, with its minimum image vector of 71 units (for the Z-component), an increase in gain was required (amplitude ratio to the 7-electrode system of 0.52).[6] The relative signal magnitude of the RLFB was found by taking a frontal plane loop at the same amplification as that used for the other two systems and then increasing the gain for a repeat of that loop and for the loops in the other two planes.

BASIS FOR LOOP COMPARISON

It was assumed that the loops obtained with the 7-electrode system were always more nearly accurate than those given by the RLFB or RAFE. A rough quantitative comparison was achieved by the same system of scoring as that used by Frank and Seiden in their comparison of the RLFB and 7-electrode systems,[6] but a refinement seemed necessary for certain cases (v.i.). Each QRS loop obtained with the RLFB and RAFE was given a score of 2, 1, or 0 in each of the following five categories, according to its similarity to the corresponding loop in the 7-electrode control.

Direction of Inscription.—A score of 2 was assigned when the directions of inscription (indicated by intensity modulation of the cathode ray) were clearly the same in corresponding loops; a score of 0 was given when these directions were opposite. When there was some doubt, as with multiple crossings, 1 point was given.

Ratio of Length-to-Width Ratios.—The ratio of the length of the maximum vector to the maximum loop width perpendicular to this vector was compared with the corresponding ratio in the 7-electrode control—the greater ratio being placed over the lesser in all cases. When the ratio was less than 1.4, a score of 2 was given; between 1.4 and 2.0 scored 1; and over 2 scored 0. (Scoring was modified in certain instances, v.i.)

Difference Between Angles of Maximum Vectors.—A score of 2 was given when there was less than 10° difference between the maximum vectors in the control and in the loop being compared with it; for differences in the range 11° to 25°, the score was 1; otherwise the score was 0. (Scoring was modified in certain instances, v.i.).

General Shape Agreement.—If the over-all shape agreement was excellent, the score was 2; if it was good, but with some minor departures, the score was 1; otherwise it was 0.

Fine Details of Shape.—If there were no discrepancies in fine detail, the score was 2. If agreement was good, but with one or two minor differences, a score of 1 was given.

In applying this system of scoring, it was occasionally found that the maximum vector of the 7-electrode loop might extend to a feature (such as a corner) clearly corresponding to a similar feature on a loop in the 4-electrode system being compared, but that such a feature in the compared loop would not lie at the tip of the maximum vector for that loop (Fig. 2). In these cases it seemed reasonable to assess correspondence between the angles of corresponding features, rather than

maximum vectors. Similar considerations also affected the determination of the length-to-width ratios in such cases. For instance, the length-to-width ratios of the two loops illustrated in Fig. 2 are equal if correspondence between various features is not utilized in designating the numerator and denominator of the ratios. While these modifications in criteria are theoretically an improvement in the method of scoring used by Frank and Seiden, their use did not greatly affect the overall results in the comparison of scores in the two systems.

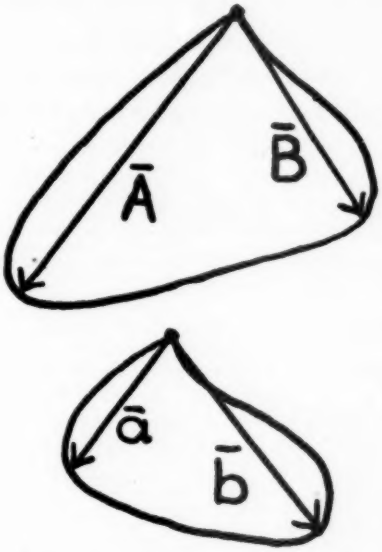

Fig. 2.—Imaginary QRS loops taken with two different lead systems to illustrate the difference between maximum and corresponding vectors. In the upper loop, which may be taken to be the control, the maximum vector is $\bar{A}$, which clearly corresponds to $\bar{a}$ in the lower loop, although $\bar{b}$ is its maximum vector. In measuring angular difference, the direction of $\bar{A}$ should be compared with $\bar{a}$ and not $\bar{b}$. In comparing length-to-width ratios, although the lower loop is clearly distorted, it would have the same length-to-width ratio as the upper loop if the length is taken as $\bar{b}$; but if it is taken as $\bar{a}$, this distortion finds expression in an altered length-to-width ratio.

RESULTS

With 40 patients, 360 different QRS loops were obtained. The results of comparing QRS loops of the RLFB and RAFE with those of the 7-electrode standard, based on the five scoring categories described above, are shown in Table I. Frontal plane scores in each category are similar in the two systems. But, in the sagittal and transverse planes, except for the scores given in the first category (direction of inscription), which are about equal, scores are higher for the RAFE. The frequency distribution of total scores is shown in Fig. 3; there is a clear shift to the right with the RAFE system. In the RLFB comparison, 13 patients received scores of less than 17, but in the RAFE only 2 scored less than this number.

Mean scores obtained for each plane with the RLFB and the RAFE, together with the mean total for the three planes, are shown in Table II. In the frontal plane, although the mean score for the RAFE is less than that for the RLFB, the difference is not significant (by Student's t-test). The probability

that such a difference could have been due to chance is greater than 0.1. However, the mean scores obtained in the sagittal and transverse planes, and the mean score for the total of the three planes, are significantly higher using the RAFE (p for the total is less than 0.01). Statistical treatment indicates that there is a 95 per cent probability of the RAFE true mean being at least 12 per cent higher than the true mean of the RLFB.* When we come to consider the likelihood of error in the individual case from use of the RLFB or the RAFE rather than the 7-electrode system, we may say that there is a 77 per cent probability that the score with the RLFB will be greater than 16, but with the RAFE the probability of obtaining a score of this magnitude, or greater, is raised to 95 per cent.†

TABLE I. NUMBER OF PATIENTS (OUT OF 40) SCORING 2, 1, OR 0 IN A COMPARISON OF QRS LOOPS IN RLFB AND RAFE WITH THE 7-ELECTRODE STANDARD

	SCORE	DIRECTION OF INSCRIPTION			RATIO OF LENGTH-TO-WIDTH RATIOS			DIFFERENCE BETWEEN ANGLES OF MAXIMAL VECTOR			GENERAL SHAPE AGREEMENT			FINE DETAILS OF SHAPE		
		F	S	T	F	S	T	F	S	T	F	S	T	F	S	T
RLFB	2	32	32	34	24	13	16	29	11	17	18	2	4	21	3	7
	1	8	7	4	8	17	11	11	12	15	22	22	26	18	28	23
	0	0	1	2	8	10	13	0	17	8	0	16	10	1	9	10
RAFE	2	31	32	38	23	21	27	29	28	19	16	7	16	15	22	19
	1	8	7	2	9	10	10	10	7	16	20	28	24	25	15	21
	0	1	1	0	8	9	3	1	5	5	4	5	0	0	3	0

F=frontal. S=sagittal. T=transverse.

The angular separation between maximum or corresponding vectors is shown as a mean angular error in Table III. The differences in the frontal plane between the two systems are not statistically significant, but in the sagittal plane, the RAFE manifests clear superiority both in its mean error, which is a quarter of that obtained with the RLFB, and in its more uniform values (lower standard error). In the transverse plane, although there is no significant difference between the means, the variance (σ^2) is significantly less with the RAFE‡

The angular difference between the maximum vectors of the test system and its control may be expressed as positive or negative, according to its direction.

*Using $\bar{x}_1 - \bar{x}_2 - t_{.05}s\sqrt{1/n_1 + 1/n_2} \leqq \mu_1 - \mu_2 \leqq \bar{x}_1 - \bar{x}_2 + t_{.05}s\sqrt{1/n_1 + 1/n_2}$, where $s^2 = \frac{(\Sigma x^2 - \Sigma x\bar{x})_1 + (\Sigma x^2 - \Sigma x\bar{x})_2}{n_1 + n_2 - 2}$; μ_1 and μ_2 are true means; $\bar{x}_1$ and $\bar{x}_2$ are sample means; and n_1 and n_2 are sample sizes.

†Based on area of normal curve. The χ^2 test of goodness of fit of the RAFE comparison scores to a normal distribution gives a probability of 0.75 that the observed discrepancies could have been due to chance.

‡By the variance ratio test, the probability is 1 in 100 that the difference is accidental.

Means of such angular differences in maximum vectors between the RLFB and the 7-electrode system have been tabulated by Frank and Seiden.[6] Table IV presents a comparison of their results with comparable data from our series. These means reveal the presence or absence of bias (a tendency for angles to be altered in one direction or the other); they do not indicate the lack of correspondence between two angles, i.e., the error. (If there were a complete absence of correspondence, there would be no tendency for the differences to be either positive or negative, so that their algebraic sum would be zero, and their mean would also be zero. On the other hand, if absolute values of the differences are taken, as in Table III, in the absence of correspondence these would be evenly distributed from 0 to 180°, and have a mean of 90°.) Confining our attention to the standard deviations in Table IV, therefore, it may be seen that these are very similar in both series. In fact, there is no statistically significant difference between them in the sagittal and transverse planes.*

TABLE II. MEAN SCORES OBTAINED WITH THE RLFB AND THE RAFE IN 40 PATIENTS

	FRONTAL		SAGITTAL		TRANSVERSE		TOTAL	
	RLFB	RAFE	RLFB	RAFE	RLFB	RAFE	RLFB	RAFE
Mean	7.9 (8.0)	7.5	5.2 (7.0)	7.2	5.8 (7.0)	7.7	18.8	22.4
σ	1.4 (1.4)	1.8	1.9 (1.6)	2.3	2.3 (1.6)	1.4	3.7	3.5
S.E.	0.22 –	0.28	0.30 –	0.36	0.36 –	0.21	0.59	0.55

S.E. = standard error.
In parentheses are the results of the RLFB evaluation by Frank and Seiden.[6]

TABLE III. MEAN ANGULAR ERROR (IN DEGREES) BETWEEN MAXIMUM OR CORRESPONDING VECTORS IN 40 PATIENTS (360 LOOPS)

	FRONTAL		SAGITTAL		TRANSVERSE	
	RLFB	RAFE	RLFB	RAFE	RLFB	RAFE
Mean Error ($\Sigma \mid x \mid$)						
n	7	8	26	6	17	14
σ	5	6	19	10	15	10
S.E.	0.7	1.0	3.0	1.6	2.4	1.5

*Variance ratios, F, for the three planes: (F) F = 2.02; (S) F = 1.51; (T) F = 1.11. Entering table of F with 39 and 103 degrees of freedom, we get approximately 1.59 and 1.95 for the 5 per cent and 1 per cent points for the distribution of F. Note that F, for the frontal plane, is above both these, indicating that there is less than 1 per cent chance that the difference in variances, in the frontal plane, of the RLFB and RAFE is accidental.

TABLE IV. MEAN ANGULAR DIFFERENCES (IN DEGREES) IN MAXIMUM OR CORRESPONDING VECTORS BETWEEN THE RLFB AND 7-ELECTRODE SYSTEM

	PRESENT SERIES (40 CASES)			SERIES OF FRANK AND SEIDEN (104 CASES)		
	F	S	T	F	S	T
Mean difference	−0.75	−13.7	−2.2	−2.1	3.5	−2.5
σ	8.5	29	22.4	12.1	23.8	20.2

The sum of the absolute magnitudes of the maximum, or corresponding vectors in each of the three planes provides an indication of the amplification required to assure distinct loops. In each of 33 patients,* the sums obtained with each system expressed as ratios of one another are shown in Table V. The RAFE required about half the amplification needed for the RLFB. The mean ratio for the RLFB/7-electrode system (0.4) is somewhat below its theoretical value of 0.52 (see section on Methods and Materials), but the mean ratio for the RAFE (0.8) is closer to its theoretical value of 0.73.

TABLE V. RATIOS OF SUMS OF ABSOLUTE MAGNITUDES OF MAXIMUM OR CORRESPONDING VECTORS IN 3 PLANES, IN 33 PATIENTS

	RLFB/7-ELECTRODE	RAFE/7-ELECTRODE	RAFE/RLFB
Mean	0.4	0.8	2.2
σ	0.08	0.032	0.5
S.E.	0.015	0.006	0.087

Figs. 4 and 5 illustrate the closer correspondence of the RAFE loops to the 7-electrode standard than the loops obtained with the RLFB. In Fig. 4, the RAFE total score was 23, but that for the RLFB was only 17. It may be noted that a score of 23, which is just above the RAFE mean, indicates a quite close correspondence, but that even a score as low as 17, which only 5 per cent of patients would fail to reach with the RAFE, does not involve a disparity likely to result in serious interpretive errors. In Fig. 5, the total score was 26 with the RAFE, but only 14 for the RLFB.

Although attempts to draw clinical conclusions from loops obtained with unfamiliar lead systems are open to criticism, and should really be postponed until a full knowledge of the normal variants of such systems has been acquired, distortion of the sagittal vectors in the RLFB gave some loops that might lead to the drawing of quite erroneous conclusions. An example of this is shown in Fig. 5 in which right ventricular hypertrophy is "suggested." Another case was strongly suggestive of anterior myocardial infarction in the RLFB, but not in

*In 7 patients a record of the amplification used for the 7-electrode system and the RAFE was not kept.

the 7-electrode system or the RAFE. In no instance did the RAFE give the kind of distortion that might be expected to lead to qualitative interpretive differences. The system of scoring does not take this kind of difference into account because it cannot be expressed quantitively.

When both the RAFE and RLFB have high scores it does not matter much which is higher, since either would be a good substitute for the 7-electrode system (although, even in these cases, the RAFE would be preferred on account of the greater convenience of electrode application and better signal-to-noise ratios).

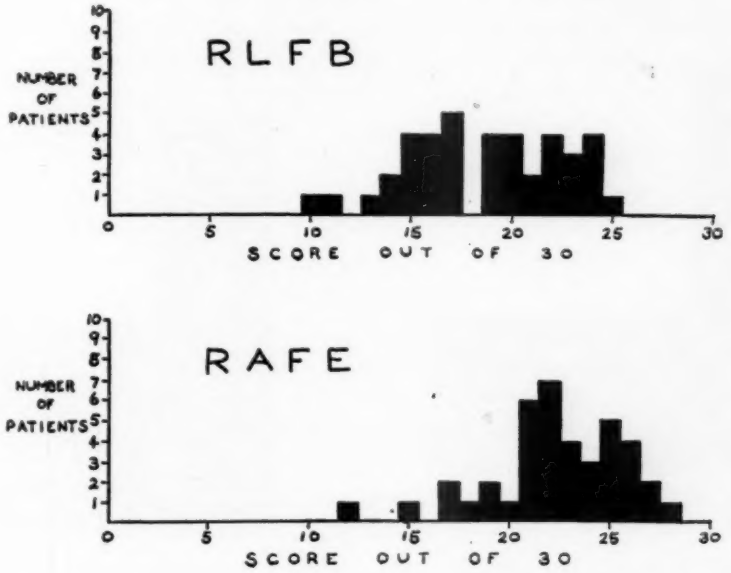

Fig. 3.—Comparison of total scores of the RLFB and RAFE systems (as measured against the 7-electrode control) in 40 patients.

On the other hand, considerable attention should be paid to low scores, for it is in these cases that errors in diagnosis are likely to arise. Looking for low scores, we see a very marked difference between the two systems (Fig. 3). With the RLFB, largely because of distortion of the sagittal forces, low scores are quite common (22 per cent scored less than 16). Thus, the view of Frank and Seiden that the loss in accuracy involved in using the RLFB outweighed any advantage gained in convenience is confirmed. With the RAFE, however, low scores were uncommon (5 per cent scored less than 16) and the differences that were noted were quantitative rather than qualitative.

DISCUSSION

The object of the present study has been to evaluate the possibility that a 4-electrode system, applicable to seriously ill patients, might furnish a more practical and convenient alternative to the 7-electrode system, currently proposed for general use, with the retention of an acceptable degree of accuracy. The RLFB has been shown to lack sufficient accuracy, even under almost ideal con-

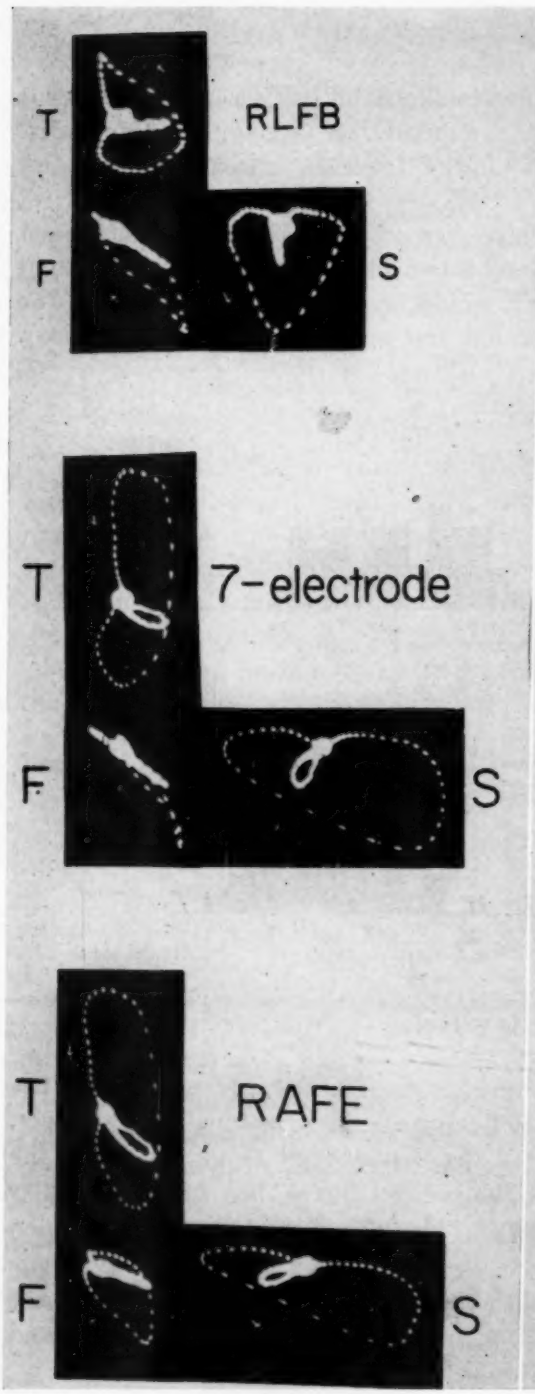

Fig. 4.

Fig. 5.

Fig. 4.—Vectorcardiograms taken on the same patient with the RLFB, 7-electrode, and the RAFE systems. The comparison score for the RLFB loops was 17, made up of 6, 6, and 5 for the F, S, and T projections, respectively. The score for the RAFE loops was 23, made up of 5, 9, and 9 for the F, S, and T projections, respectively. The average score for the RAFE system was 22.4, and 95 per cent of patients gave RAFE loops scoring more than 16.

Fig. 5.—Vectorcardiograms taken on a normal patient with the RLFB, 7-electrode, and RAFE systems. The RLFB scored 14 (F, 8; S, 6; T, 0) and the RAFE scored 26 (F, 8; S, 9; T, 9). The correspondence between the RAFE and the 7-electrode control is close but the sagittal and transverse loops of the RLFB are displaced and distorted, and "suggest" right ventricular hypertrophy.

ditions.[6] The results of the present comparison show that the RAFE 4-electrode system tends to depart much less from the 7-electrode standard than does the RLFB, when these systems are applied with minimal disturbance of the patient.

There are some differences between the results of the present comparison of the RLFB and the 7-electrode system and those reported by Frank and Seiden. For example, we obtained mean sagittal- and transverse-plane scores of 5.2 and 5.8, respectively, whereas they obtained scores of 7 for both planes (Table II, in which the results of Frank and Seiden are shown in parentheses). Part of this discrepancy is due probably to variation in technique dictated by a closer adherence, in the present study, to conditions that would prevail during the examination of very sick patients. It should be noted, however, that two out of the five scoring categories, viz., general shape agreement, and fine details of shape, involve subjective criteria. When a nonsubjective evaluation, such as the standard deviation of the angular differences in maximum or corresponding vectors, is considered (Table IV), the differences for the sagittal and transverse planes are not significantly different in the two series; despite this, the total mean scores, which include subjective criteria, are different. Note, also, that although the RLFB-7-electrode angular agreement in the frontal plane was better in our series ($\sigma = 8.5$) than in that of Frank and Seiden ($\sigma = 12.1$), the mean total scores are equal (Table II). This suggests that we have been a little more severe than they in allotting scores for general shape and fine detail.

When the RLFB loops showed a marked departure from those obtained with the 7-electrode system, the difference was due largely to errors in the recording of sagittal forces. Frank and Seiden reported that with the RLFB, muscle-tremor interference was severe in many cases, giving difficulties which tended to offset its practical advantages.[6] They also felt that, in any event, failure to obtain a consistently satisfactory p_z (i.e., sagittal lead) seemed to rule out that system. In using the anterior mid-chest instead of the back, the RAFE gains not only in convenience, but also in signal magnitude (with reduction of muscle-tremor interference by one half) and in the accuracy of the p_z lead.

SUMMARY

Two 4-electrode, VCG lead systems have been compared, under clinical conditions, with a theoretically more accurate 7-electrode system, in 40 patients. All systems used the appropriate resistance-combining networks embodying correcting factors determined from torso models. One of the 4-electrode systems, the RLFB, which was based on the Wilson tetrahedron, had been compared with the 7-electrode system by Frank and Seiden, and had been rejected on the grounds of insufficient accuracy. The other 4-electrode system, the RAFE, was designed, unlike previous systems, to give optimal convenience of application. The results showed:

1. Under conditions obtaining with ill patients, the RAFE showed a highly significant advantage with respect to accuracy as compared with the RLFB. This was due largely to improvement in the recording of sagittal components.
2. The signal-to-noise ratio with the RAFE was close to that obtained with the 7-electrode system and much greater than that with the RLFB.

CONCLUSION

The results indicate that the optimal convenience provided by the RAFE lead system is achieved at a relatively small cost in accuracy and signal magnitude. They suggest the use of this electrode arrangement at least in seriously ill patients, who would be unduly disturbed by the application of the 7-electrode system.

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Myocardial Ischemia and Its Effect on the Standard Limb Leads of the ECG

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INTRODUCTION

The significance of low voltage of the QRS complex in the standard limb leads has never been fully understood. The existence of small QRS deflections is known to occur in many clinical conditions, such as chronic constrictive pericarditis,[1] right-sided cardiac failure,[2] scleroderma,[2] myocardial disease,[3] anemia,[4] myxedema,[5] pulmonary pathology,[6] and metabolic disease.[2] Low voltage has been produced experimentally by exsanguination of animals,[7] transfusing animals,[8] ligation of the vena cava,[9] ligation of the coronary sinus,[10] injecting saline into the pericardial sac,[9] and in the presence of edema.[11,12] The explanation for low voltage of the QRS complex is further confused by the statement that it occurs in normal hearts.[13,14] Observers[3,13,15-18] are divided as to the importance that should be attributed to this finding. The purpose of this study is to show that, under certain circumstances, low voltage of the QRS complex in one or more of the standard limb leads is associated with ischemia of cardiac muscle and/or a decrease in coronary blood flow to the myocardium.

MATERIAL AND METHODS

The studies were divided into 4 groups of animal experiments. One clinical case (postmortem) was used in comparison with the results of the animal experiments.

Mongrel dogs that weighed approximately 15 kilograms each were anesthetized with veterinary Nembutal. Immediately after endotracheal intubation with attachment to an intermittent positive pressure apparatus, the left thorax was entered through an incision in the left fifth intercostal space.

Experiment 1.—Ten animals were subjected to a revascularization procedure,[19] consisting of cardiopneumonopexy and lingular vein ligation. The pericardium was incised and a 30 per cent acriflavine solution was painted over the distribution of the anterior descending coronary artery. The lingula vein was doubly ligated with 3-0 black silk. The lingular lobe was then sutured with interrupted 5-0 black silk directly onto the exposed surface area of the myocardium supplied by the anterior descending artery. Twenty-two to 68 days later the anterior descending

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branch of the left coronary artery was ligated and divided adjacent to the origin of the circumflex artery. In previous experiments it was determined that in 30 to 60 days the collateral vessels were of sufficient size to deliver the minimum amount of blood necessary to prevent death, but not to prevent development of the ischemic pattern.

Experiment 2.—Another series of 10 normal animals was subjected to partial ligation of the circumflex branch of the left coronary artery. The circumflex branch was constricted partially by two snug ligatures, and then later the ligatures were released. Such ligatures were placed both proximal and distal to the origin of the left marginal branch of the circumflex artery.

Experiment 3.—The pericardial sacs were each filled with from 90 to 120 ml. of saline in 5 additional animals. Later, the pericardial sacs were incised, permitting the saline to flood the thorax.

Experiment 4.—Two revascularized animals that had been subjected previously to complete anterior descending coronary artery ligation were studied further. The circumflex artery was constricted in two regions of its distribution. First, the anterior distribution of the circumflex was constricted and then released. Next, the posterior distribution of the circumflex was constricted and then released. Later, the anterior and posterior distributions of the circumflex coronary artery were constricted simultaneously for 45 minutes. Removal of the ligatures completed the experiment.

Controlled electrocardiographic tracings were taken, using the standard limb leads in each of the 4 groups of animal experiments.

In the series with complete occlusion of the anterior descending coronary artery (Exp. 1) the electrocardiograms were taken immediately after occlusion and at varying intervals up to 120 minutes after occlusion. Tracings were again taken at the time the animals were sacrificed. In the temporary partial closure experiments (Exp. 2) studies of the electrocardiograms were taken during constriction and immediately after release of the constriction. In the pericardial effusion series (Exp. 3) the electrocardiograms were taken before and after injection of the saline, and after incision of the pericardial sac. In the revascularized animals whose anterior descending coronary artery had been occluded previously (Exp. 4) the electrocardiograms were taken during constriction, and immediately after release of the circumflex artery. Standardized Sanborn electrocardiograms were used, and neither the position of the electrodes nor the animals was changed during the experiments.

RESULTS

Experiment 1.—All 10 revascularized animals showed diminution of the QRS complex as an initial response after complete occlusion of the anterior descending coronary artery. The animals with the best functional collateral circulation demonstrated only QRS diminution. The change in the electrocardiogram was dramatic in all animals. Fig. 1 is a tracing which demonstrates the QRS diminution after anterior descending coronary artery ligation. Note the appearance of the normal electrocardiogram 31 days later when the animal was sacrificed.

Experiment 2.—When the circumflex artery was constricted partially in 10 normal dogs, the voltage was lowered in all experiments. After the release of the constriction, the voltage was restored to the control level in 8 dogs. In 2 animals removal of the constriction did raise the voltage again but not to the original level. This finding was interpreted by us as a persistence of impairment to the coronary flow. Other findings such as T-wave changes were noted, but they are not within the scope of this discussion. Fig. 2 is an electrocardiogram illustrating two stages of constriction and steps in voltage reduction of Leads II and III. Note the increase in the amplitude of the R wave in Lead I and the decrease in voltage of the R wave in Leads II and III immediately after partial constriction of the circumflex coronary artery. The S-T segments in Leads II

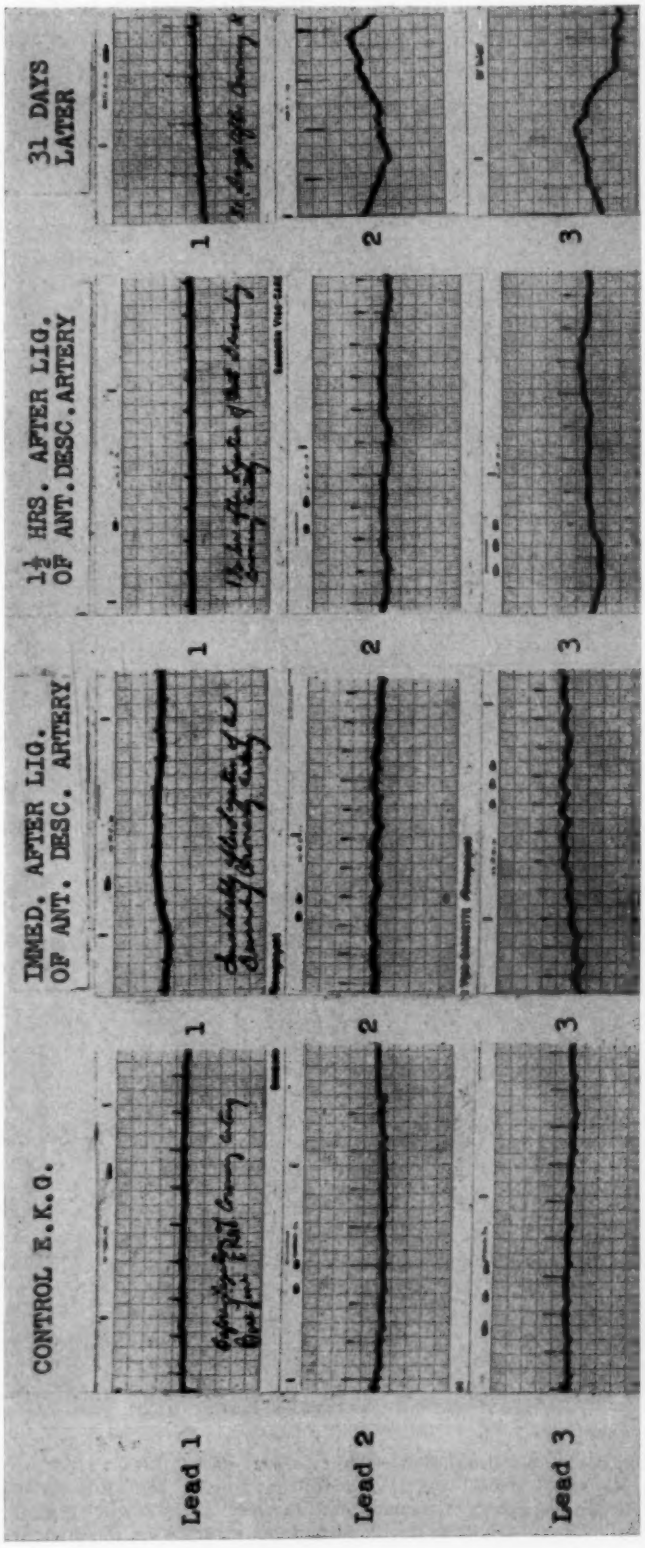

Fig. 1.—The control ECG was taken 45 days after the revascularization procedure demonstrated normal R-wave amplitude. Immediately after ligation of the anterior descending coronary artery, a voltage drop of the QRS complex was noted in Lead I. The ECG taken 1½ hours later continued to show low voltage in Lead I. The final ECG taken 31 days later revealed normal voltage.

and III had not become elevated until additional constriction was made on the circumflex artery. The final tracing demonstrated a decrease in R-wave amplitude in Lead I and increased QRS voltage in Leads II and III when the ligatures around the circumflex coronary artery were removed.

Experiment 3.—The pericardial effusion study showed that voltage could be

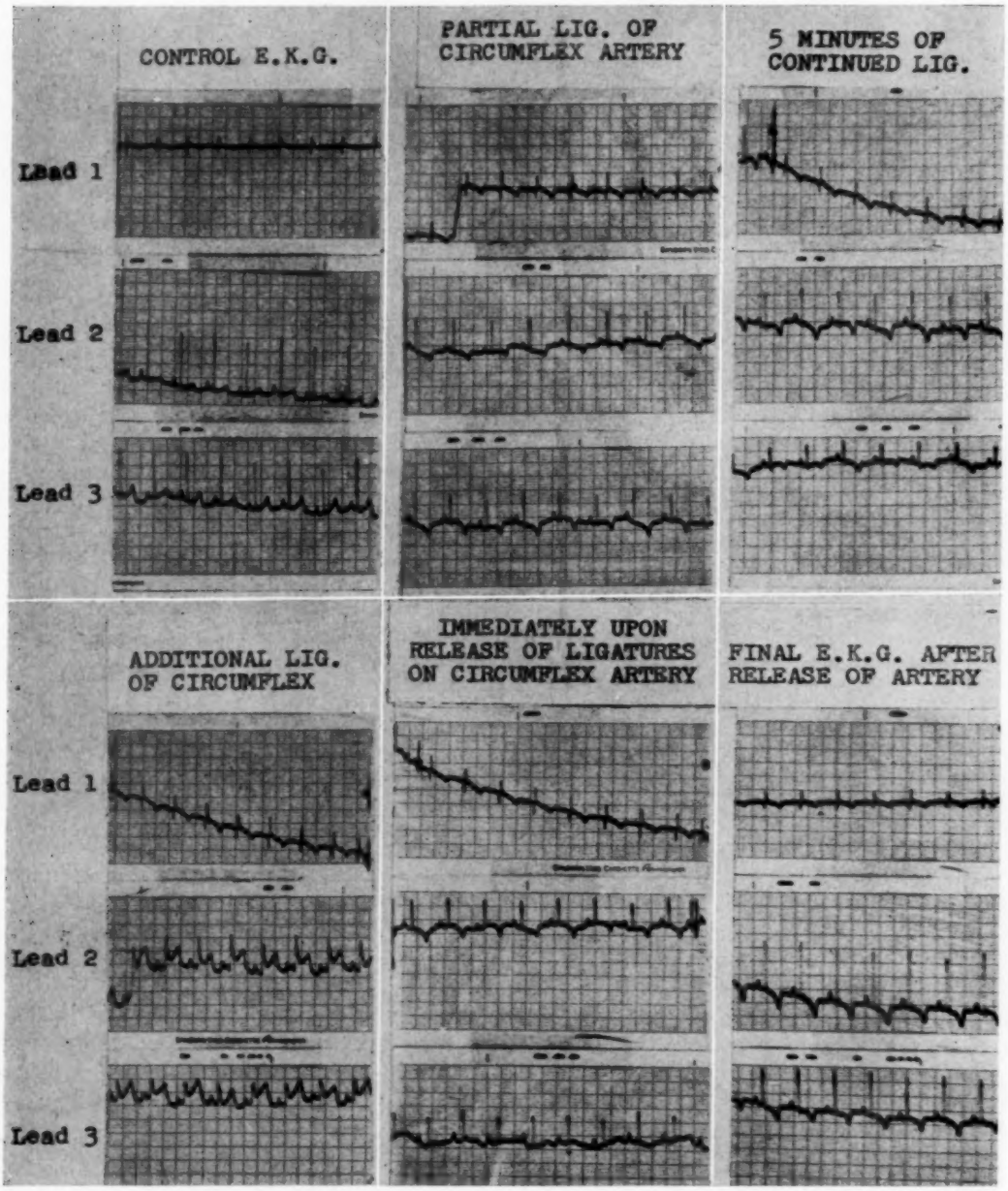

Fig. 2.—Partial ligation of the left circumflex coronary artery on the *lateral* aspect of the animal's heart revealed a drop in voltage in Leads II and III. Note that the S-T segments became elevated in Leads II and III after the circumflex artery was constricted further. The R-wave amplitude remained low in Leads II and III until the constrictions on the circumflex artery were released.

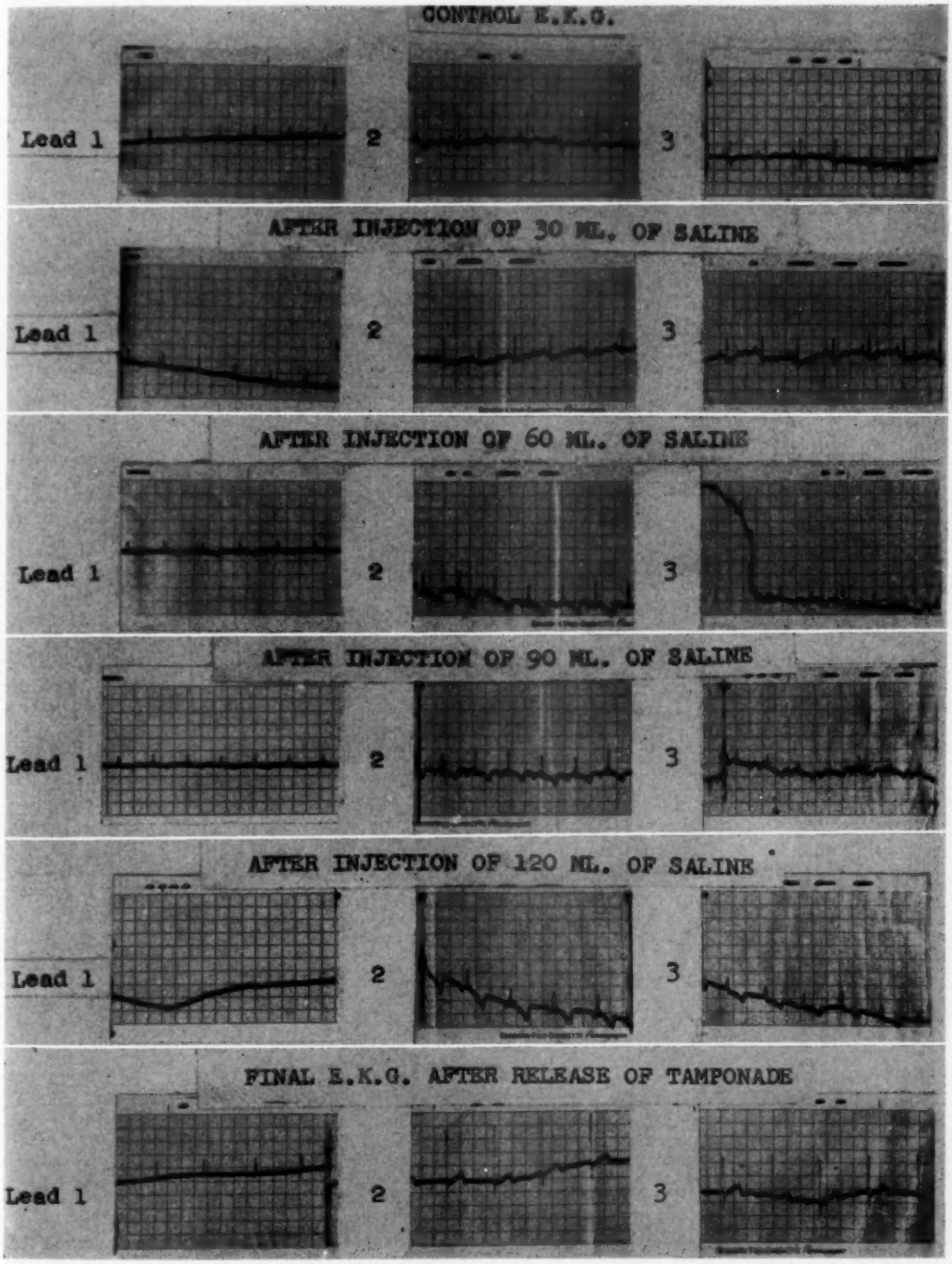

Fig. 3.—In this experiment a stepwise lowering of voltage was produced by injecting saline into the pericardial sac. Note the voltage return after release of the tamponade. Leads II and III have higher voltage after release of the tamponade. The saline in the thorax after incision of the pericardial sac had no shunting effect on the QRS voltage of the *standard bipolar limb leads.*

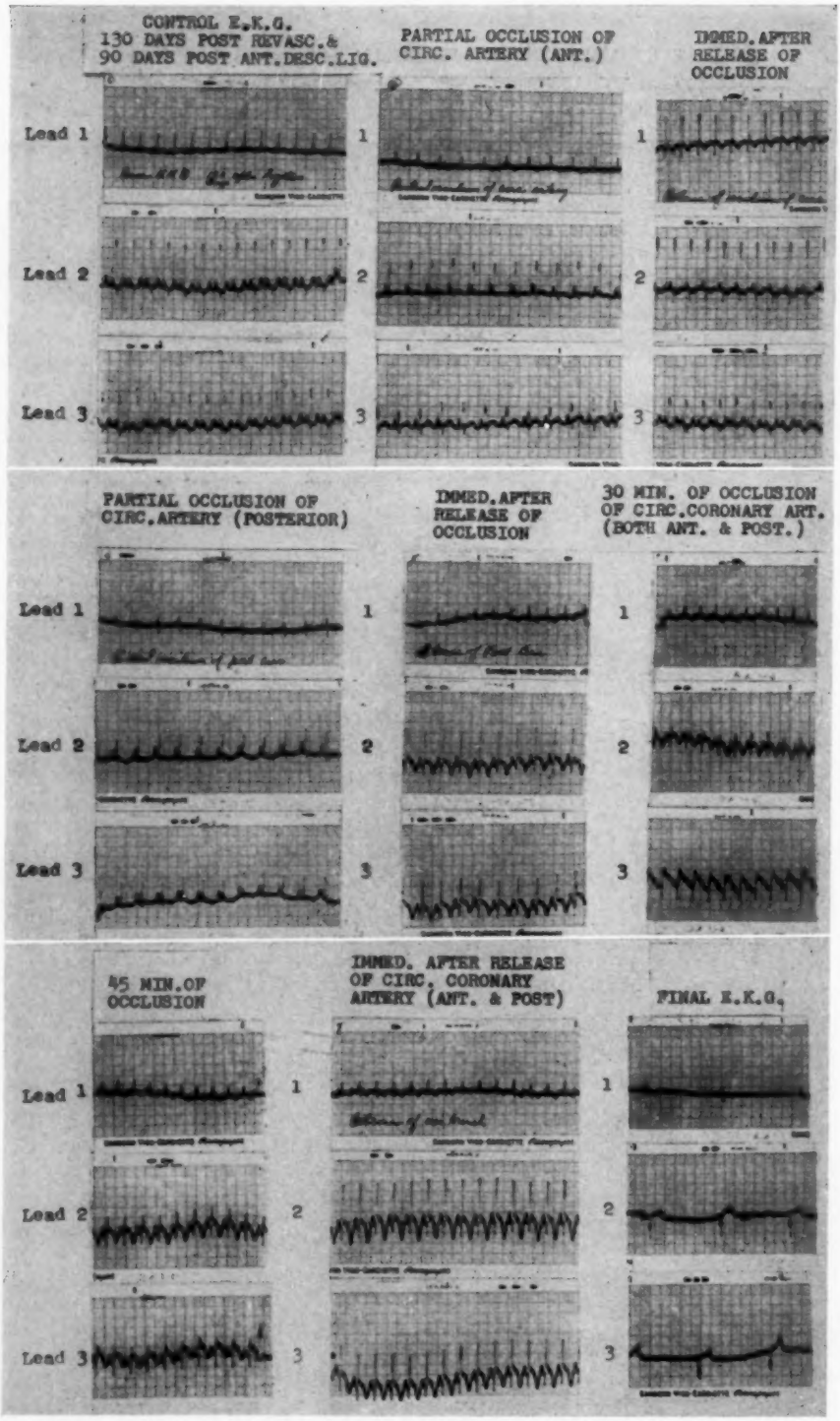

Fig. 4.—This experiment was performed 130 days later on a previously revascularized animal that had had its anterior descending coronary artery ligated for 90 days. First, the anterior circumflex artery was constricted partially and then released. Next, the posterior circumflex was constricted partially and released. Then both the anterior and posterior distributions of the circumflex artery were constricted partially for 30 and then 45 minutes. After 45 minutes of constriction, the ligatures were released. The ECG taken immediately after the release of constriction showed re-establishment of the voltage. The final tracing taken probably represents one of three possibilities, namely: (1) A-V nodal, arising from lower (ventricular) end of A-V node, the P wave being retrograde in character and deforming the T-wave segment; (2) middle nodal rhythm, with the inverted wave representing the T wave and the normally observed P wave being buried imperceptibly within the QRS complex; or (3) inverted wave representing a T wave with the ventricular response being actually idioventricular in origin.

lowered by the instillation of saline within the pericardium. A stepwise diminution in the R waves can be seen in all three standard bipolar limb leads illustrated in Fig. 3. Note that T-wave changes occurred simultaneously with a decline in voltage. In addition, one can see that the voltage did not remain lowered but returned to the control level even when the pericardium was incised and saline flooded into the left pleural cavity. The voltage of 1 animal remained low after release of the effusion. The voltage continued to be low even though the thorax was sponged dry.

Experiment 4.—Partial constriction of the circumflex artery after anterior descending coronary artery ligation in 2 revascularized animals showed diminution of the R waves. The electrocardiographic tracings (Fig. 4) demonstrated lowering of the R waves in all three standard bipolar limb leads when the anterior distribution of the coronary artery was constricted. After the constriction was released, it can be noted that Lead I demonstrated an increase in voltage of the R wave beyond the control level. The R-wave amplitude in Lead II increased to the previous level. In addition, the QRS voltage in Lead III increased, but not to the height obtained by the control. Note that the occlusion of the posterior distribution of the circumflex coronary artery also caused a drop in amplitude of the R waves in the three standard limb leads. After the

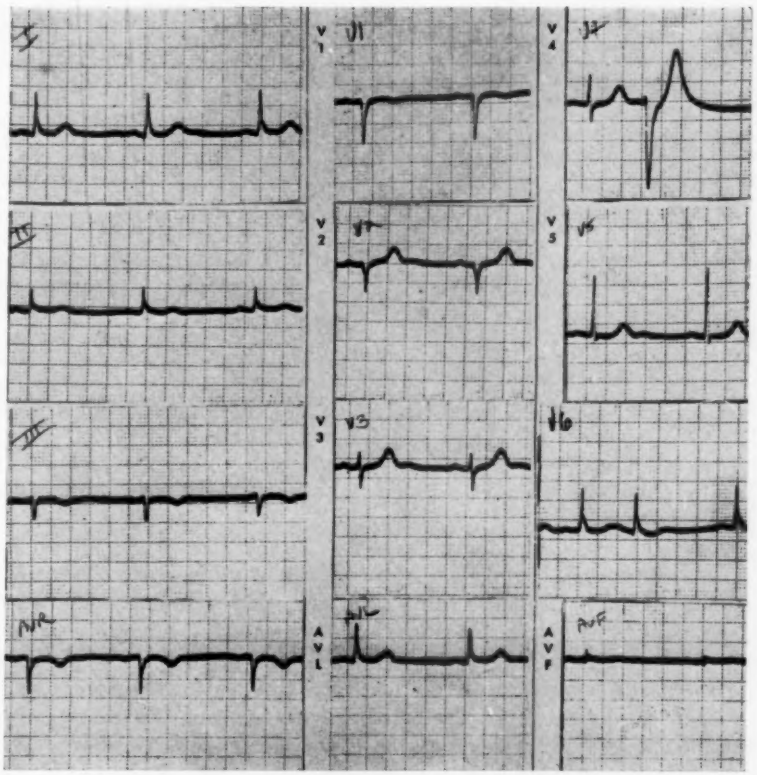

Fig. 5.—Patient E. B.'s electrocardiogram shows low voltage in Leads II, III, and aVF. Note the absence of R wave in V_2 compared to minimal upright deflection of the R wave in Lead V_1 and equiphasic QRS in Lead V_3.

constriction was released, Leads II and III demonstrated an increase in voltage of the QRS complex. However, the voltage in Lead I remained low. After anterior and posterior distributions of the circumflex coronary artery were both constricted for 30 minutes and then 45 minutes, a drop in voltage in Leads II and III was noted. The release of the constrictions again permitted the amplitude of the R wave to reach the control level. However, Q waves became markedly increased in Leads II and III. The final tracing demonstrates an abnormal rhythm which developed 15 minutes after the constrictions were released. This rhythm developed without any other manipulation of the dog's heart.

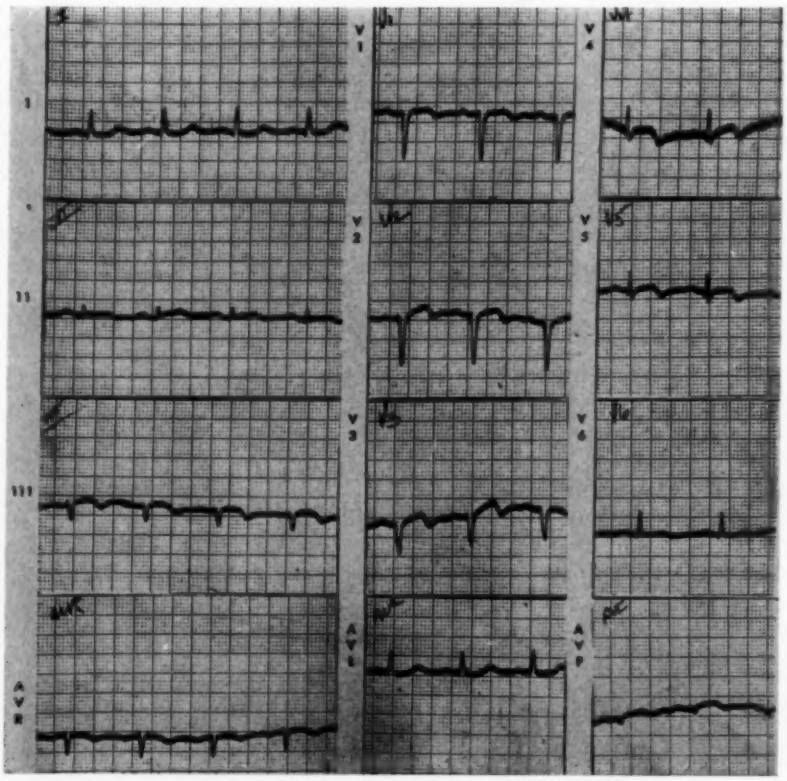

Fig. 6.—Electrocardiogram, taken 6 months after Fig. 5, demonstrated a decrease in voltage in Leads I and II, in the *bipolar limb leads*, as well as in the unipolar limb Lead aV_L and the unipolar precordial Leads V_3 through V_6.

CASE.—E.B., a 64-year-old Negro woman, was admitted to the hospital because of epigastric distress and symptoms of congestive failure. Fourteen years previously she was diagnosed as having diabetes mellitus. Also at that time thyroidectomy was performed because of thyrotoxicosis. Over the past 14 years she had been treated with varying doses of insulin and regulation of diet; for the past 6 months she had received 12 units regular and 16 units protamine zinc insulin, plus a 1,000-calorie diet. Except for occasional syncope and exertional dyspnea, the patient had been asymptomatic. There was no history of retrosternal pain.

Physical examination on admission revealed a rectal temperature of 101°F., blood pressure of 100/80 mm. Hg, and a heart rate and peripheral pulse of 80. The lungs revealed fine moist râles in both bases. The apex beat of the heart was heard in the mid-clavicular line. A Grade 2 rough systolic murmur was heard at the aortic area. The heart sounds were diminished except

for the pulmonic sound which was increased in intensity. The liver was not enlarged. There was no pitting edema. The Homans' signs were negative. Babinski's and Hoffmann's signs were negative, and the deep reflexes were normal.

Laboratory Findings.—The cholesterol ranged from 318 to 460 mg. per cent over the past 6 months; sugar was 161 mg. per cent; CO_2, 39.0 volumes per cent. Chlorides, 89 mEq.; sodium, 140 mEq.; potassium, 5.2 mEq. Hemoglobin was 11.8 Gm. per cent. Hematocrit, 51 per cent; WBC, 14,000. Urinalysis: 1.013, yellow, acid, protein—2 plus, sugar negative, casts 3-6/leukocytosis-promoting factor.

On the third day of admission the patient went into shock and expired.

Post-Mortem Gross Pathology of the Heart.—The heart weighed 360 grams. At the apex there was an old infarction, measuring 2 × 2 cm., which caused marked thinning of the myocardium. The latter finding is, by one criterion, an actual aneurysm. Another infarct was present throughout the entire septum, extending from the anterior to the posterior wall. The remainder of the ventricular myocardium was normal except for the infarctions noted above. The right coronary ostium was reduced to a pin-point opening. However, the right coronary artery and all of its terminal branches were patent throughout and of normal diameter. The circumflex branch demonstrated 85 per cent occlusion, whereas the anterior descending showed 65 per cent occlusion 2 cm. distal to its origin. The valves were thin and competent except for the aortic valve which presented sclerotic cusps with multiple granules of calcium.

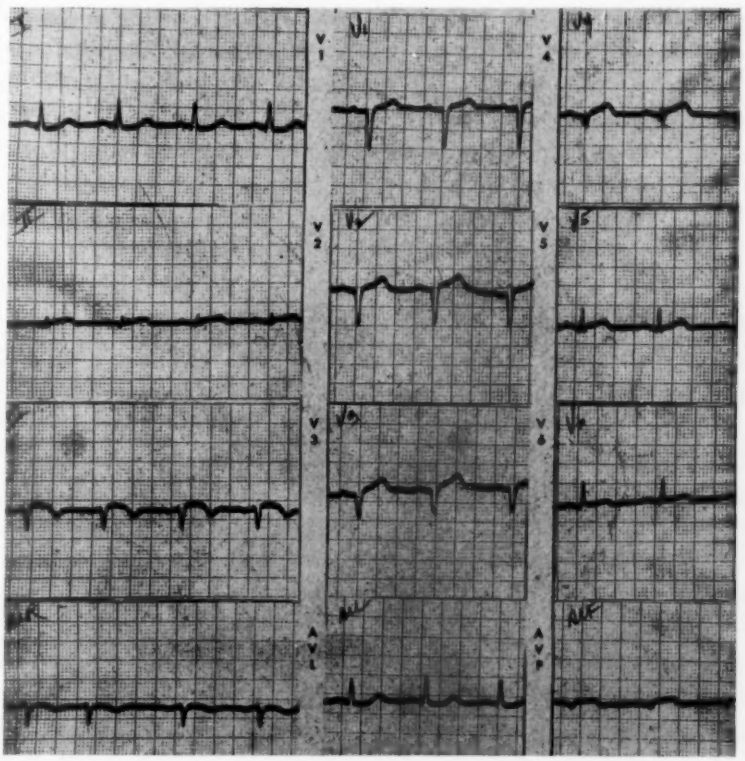

Fig. 7.—Electrocardiogram taken 1 day after Fig. 6 reveals a still further diminution in voltage of the R wave in Lead V_4 with a resultant W-shaped QRS complex, certainly not explainable on the basis of simple electrode misplacement. The location of the coronary block was thought to be almost complete in the circumflex artery near the bifurcation from the left coronary artery. The anterior descending artery was thought to have diminished blood flow to a lesser extent than the circumflex artery. Extensive damage was thought to be present in the septum by virtue of the findings in the chest leads.

Cause of death: Acute myocardial infarction superimposed on a previous myocardial infarction was considered as the cause of death in this patient.

Fig. 5 is a tracing used as the patient's electrocardiographic base line. This tracing was taken 6 months before the patient's death. Leads II and III showed low voltage. Lack of an R wave was noted in V_2. Occasional premature contractions were noted. An old myocardial infarction seemed to be present in the septum.

Fig. 6 is an illustration of the tracing taken on the patient 6 months after Fig. 5. Note the diminution of voltage which occurred in Leads I and II. Associated lowering in voltage in chest leads had additional significance. S-T segment and T-wave abnormalities provided further evidence that coronary insufficiency existed.

Note the further decreased amplitude of the R wave which is demonstrated in Lead II (Fig. 7). On the basis of the progressively decreased voltage of the QRS complex demonstrated in Lead II, it was thought that obstruction of the circumflex branch of the left coronary artery was almost complete. A decrease in the lumen of the anterior descending artery was also anticipated because the voltage of the QRS complex in Lead I was lowered considerably. No change in voltage occurred in Lead III. However, that type of configuration has been noted, by us, to occur when infarction is present in the posterior portion of the septum.

DISCUSSION

Today there are two basic theories used to explain the amplitude of the R wave in the standard limb leads:

1. According to the first theory, the cardiac chambers contain a certain volume of blood which acts as a shunt for the electrical currents passing through the heart.[9] It has been found that transfusion of animals causes a decrease in voltage of the QRS complex, whereas replacing the blood with olive oil causes an increase in voltage.[8] In addition, when the ventricular chambers were permitted to empty in a perfused frog, this resulted in an increased height of the R wave.[20]

2. The second theory maintains that there is a blockage of electrical currents because of the insulating effect of the fluids or the air-containing tissues which encompass the heart.

The first theory loses some of its validity when tested by in vitro experiments, because coronary flow most often is a variable factor. In addition, exsanguination of animals results in voltage decrease, whereas restoration of the blood volume re-establishes the voltage of the QRS complex[7] to the prior level.

Pathologic states to which the second theory seems more applicable include myxedema and pericardial effusion. However, in some experimental and clinical pericardial effusions the voltage remained low immediately following aspiration of the pericardial fluid. Some myxedematous patients have associated myocardial disease and many exhibit pericardial effusion. Constrictive pericarditis presents an enigma because patients with pericardial constriction when relieved of their pericardial adhesions may often reveal a drop in voltage of the QRS complex.

All disease processes showing low voltage in one or more of the standard ECG limb leads cannot be explained fully by either theory or by a combination of the two. It would be more convenient to explain instances of low voltage on the basis of a concept involving a common factor.

It is not implied in this discussion that amplitude of the R wave is not dependent upon the electromotive force developed by the contracting myocar-

dium. However, the authors have formulated a hypothesis which stipulates that progressive occlusion of a coronary vessel produces a gradual decrease in voltage in the standard limb lead for the area of the myocardium affected. If the myocardium is ischemic throughout, then all three standard leads are of decreased amplitude. While this diminution in blood flow is taking place, new collateral anastomoses are developing from adjacent channels.

When periods of relative coronary artery insufficiency exist, such as during marked tachycardia, hemorrhage, shock, and abdominal catastrophe, there may be a marked drop in voltage of the QRS complex. This drop in voltage can occur even though the coronary arteries are free from occlusive disease. Infarction may not be evident by routine hematoxylin-eosin stain at post-mortem. However, it is entirely possible that death is caused by anoxia to the myocardium in many of these patients.

In complete experimental occlusion of the anterior descending artery, the voltage remained lowered until channels were large enough to increase the blood flow and/or blood volume to the myocardium. In the partial-constriction-release series the low-voltage changes were reversible. This seems to us to indicate that voltage can be altered by coronary flow. In the pericardial effusion experiment, the T wave became inverted simultaneously with diminution of the QRS complex. Fluid in the pleural cavity after release of the tamponade did not keep the voltage lowered. It is possible that the pericardial effusion caused a stasis of coronary blood flow; however, the myocardium did not appear cyanotic. It has been reported that constriction of the coronary sinus[10] causes a drop in voltage of the QRS complex with cyanosis of the myocardium. The authors repeated this experiment and are in complete agreement.

This concept, of voltage being related directly to coronary blood flow, has interesting possibilities to offer the cardiologist in that it can be employed to localize the cardiac pathology. For patients having only one coronary artery involved actively in the disease process, it could be of use to the cardiac surgeon who performs coronary endarterectomy procedures. It might also aid in evaluating the prognosis and therapy of cardiac patients.

Saphir and associates[21] have stated that infarction did not occur when only one main artery was involved in the arteriosclerotic process. The latter authors, as well as Blumgart and associates,[22] revealed that complete coronary artery occlusion can occur without actual myocardial infarction and vice versa. These observations would appear to be in complete agreement with the findings reported in the present communication. It should be stated that the concept of low voltage being associated with myocardial disease has been noted by other observers.[23,24] However, the importance placed on the finding of low voltage in one standard limb lead has never been specifically emphasized as indicative of heart pathology. The experiments described in this paper tend to substantiate that when voltage is low in one or more leads, it is frequently associated with, and secondary to, myocardial ischemia.

On the basis of our animal experiments and the clinical case described, the authors consider any sudden decrease in voltage as pathologic even though there may be no other abnormal electrocardiographic finding.

SUMMARY

This experimental study was based on a series of 25 dogs. Our results indicate the amplitude of the QRS complex in the standard limb leads could be lowered by decreasing coronary blood flow.

Ten revascularized dogs showed diminished voltage changes after complete occlusion of the anterior descending coronary artery.

Ten normal dogs showed rapid changes that were reversible: first, a lowering of the QRS complex during constriction and, then, a change back to normal after release of the coronary arteries.

Pericardial effusion was produced in 5 dogs, with a subsequent decrease of the QRS voltage. Releasing the fluid into the thorax did not keep the voltage lowered.

Two of the revascularized animals with anterior descending artery occlusion were later studied during constriction and release of the circumflex coronary artery. These animals also demonstrated reversible voltage changes.

Finally, one clinical case was presented to show the practical application of the concepts presented in this paper. It is our belief that the experimental results reported above can shed considerable light on many an obscure clinical cardiac picture.

We wish to express our appreciation to Dr. William L. Martin, Professor in the Department of Surgery, for helpfulness in the preparation of this paper, and to Dr. Franklin C. Massey, Assistant Professor of Medicine and Chief of the Cardiac Clinic, for the final interpretations given on ECG tracings.

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Ventricular Excitation in Experimental Left Bundle Branch Block

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Experimental bundle branch block (BBB) has been a means of studying the role of conduction tissue in ventricular excitation, particularly as applied to clinical conditions. When Lewis[1] first established electrocardiographic criteria for right and left BBB, he concluded that the increased duration of the QRS complex in BBB resulted mainly from the increased time required for septal activation. He also believed that spread through the affected ventricle was altered. Wilson[2] and Barker,[3] in studying the excitatory pathways of the heart and their relationship to the QRS complex, noted that Lewis had confused right and left BBB. They corrected this error, and established the presently accepted electrocardiographic criteria for presence of these conduction defects.

More recently, several groups have studied the mechanism of ventricular activity in BBB using intracavity leads, esophageal leads, and records of ventricular mechanical activity. Wolferth,[4] Braun-Menendez,[5] and Smith[6] noted delay in mechanical contraction of the blocked side. Wener and his co-workers[7] agreed with Sodi-Pallares,[8,9] Rosenbaum,[10] and Smith[11] that the initial intracavity potential was reversed from negative to positive on the homolateral side in experimental BBB.

Although agreeing with Lewis[1] that altered septal excitation was the major cause of the prolongation of the QRS during BBB, Smith and his co-workers[11] proposed that the conduction system was also altered so that mural activation proceeded by less direct Purkinje pathways than those normally traversed. Rodríguez[12] and Sodi-Pallares,[13,14] however, believed that the speed, direction, and sequence of activation in the free ventricular wall was unchanged in BBB, and ascribed the changes in the QRS complex to "delay" of conduction and decreased speed of activation in the interventricular septum.

Using multichannel recording techniques, Erickson and his co-workers[15] studied septal and mural activation in right BBB, and dealt with many of these

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controversial points. With similar recording techniques, a more detailed study of ventricular excitation in left BBB was undertaken in the hope of further resolving some of the points in question and of elucidating the mechanisms of BBB.

MATERIALS AND METHODS

Nine dogs weighing 6 to 10 Kg. were placed under barbiturate anesthesia, and maintained by artificial respiration. A sternum-splitting procedure gave a wide exposure of the heart, which was cradled in the pericardium to make the left ventricle accessible. Warm physiologic saline was applied to the epicardium throughout an experiment.

The recording apparatus, described in detail elsewhere,[16] consisted of multipolar electrodes, multichannel oscilloscope, and Grass camera. The electrodes consisted of 15 fine insulated wires, staggered along a central shaft, with their bare tips exposed at 1-millimeter intervals. A bank of 16 oscilloscopes displayed the activity at the electrode tips. Time pips at 5-millisecond intervals were fed into all channels simultaneously from a master oscillator. A switch permitted the taking of unipolar records (potential between each terminal and an indifferent body surface point) or bipolar records (difference between adjacent terminals).

The fifteenth oscilloscope was used to record a fixed time-reference potential, obtained from an electrode inserted in the wall of the right ventricle. The sixteenth oscilloscope recorded a Lead II electrocardiogram.

Recording electrodes were inserted into the myocardium to cover all areas of the septum and walls. Most often, planes parallel to the base were used, but some mid-coronal, anterior, and posterior left ventricular placements were also utilized. India ink or colored threads identified electrode paths for anatomic-physiologic correlation.

After normal excitation had been recorded, a specially designed knife was inserted through the left ventricular myocardium, and directed toward the aortic valve. The knife was advanced until its tip was felt by a finger placed posterior to the ascending aorta. The tip was then withdrawn a few millimeters, and the blade was rotated to incise the septal endocardium near the junction of the posterior and right anterior cusps. Potentials recorded on an electrode in the interventricular septum and a Lead II electrocardiogram were monitored to determine when a complete block had been produced. Normally the septum is excited by double envelopment from both endocardial surfaces. After block it is excited entirely from the right. This change in direction of excitation can be easily detected by an electrode across the septum. When the electrocardiogram is concurrently changed, we can be sure that left bundle branch block (LBBB) is present. When block was obtained, the pattern of excitation was again plotted.

All potentials recorded were first related to the time-reference potential and then, by a fixed time correction, to the beginning of the QRS. Although there were variations between the various experiments, the usual experiment included about 20 electrode insertions, i.e., records from about 300 ventricular points.

RESULTS

Figs. 1 and 2 show potentials recorded on one insertion of the multipolar electrode across the mid-central interventricular septum before and after LBBB. A negative potential gave a downward deflection in a unipolar lead.

In the unipolar control records (Fig. 1,*A*), left cavity potentials (Channels 1 and 2) show only negativity, indicating predominance of activity receding from that cavity through the septum and left wall. The right cavity potential (Channel 14) shows a slight positive deflection before the dominant negative deflection. This early positivity reflects the initial activity on the left. From Channel 3 through Channel 13 there is a rapid negative component indicative of local depolarization. While the initial component in Channels 4 and 5 is

negative, the remaining channels show a short, low-voltage, positive wave preceding the rapid negative deflection. The slow, prominent negative component has a duration of 25 to 35 msec.

Following LBBB, an initial positive potential lasting some 40 msec. was recorded on Channels 1 through 4 (Fig. 1,*B*). This positive potential resulted from spread of activation from right to left across the septum. The positive wave, although it decreased in magnitude, persisted up to Channel 13. Channel 14 showed only a negative deflection, in contrast to the small initial positivity recorded before block. The shape of the potential on all channels also changed. Plateauing of the slow component increased the duration of the negative wave to 55 msec., 20 msec. longer than in the normal record. This negative potential probably represents late activity, receding through the left wall.

In the bipolar control records (Fig. 2,*A*), Channels 3 through 8 showed a downward deflection, indicating activation from electrode tip to base, i.e., from left to right across the septum; while Channels 9 through 13 showed upright deflections, indicating movement of activity from right to left across the septum. This excitation pattern is characteristic of the normal double envelopment of the septum. The records on Channels 2 and 14 are from electrodes near the endocardium, in the left and right cavities, respectively, and show some evidence of nearby muscular activity.

After LBBB, septal activation was entirely from the right as shown by the bipolar records in Fig. 2,*B*. Channels 3 through 8 now displayed upright deflections indicating excitation from the right, but the shape of the potentials on Channels 9 through 13 and their relationship to the time-reference potential were unaltered (Fig. 2,*A*). The earliest point of depolarization was on the right endocardium (Channel 3). These records demonstrate that there is no delay at the junction of the septal tissues previously activated from the right and from the left (between Channels 8 and 9).

Fig. 3, top, shows the sequence of depolarization in a heart cut by 4 planes parallel to the base. The advance of the wave front (darkened area) through the ventricles is shown sequentially. Normally, a central region of the left septal endocardium is excited first. A few milliseconds later the right endocardium is excited, followed by depolarization of tissues surrounding the cavities. The wave front then moves apically and in a circular fashion around each cavity, toward the epicardial surfaces. Ventricular invasion is virtually complete 20 to 30 msec. after the onset of QRS; the basal septum and the posterior wall are the only portions which remain to be excited. A more detailed description of this process can be found elsewhere.[17] Noteworthy points in this picture of normal excitation are (1) double envelopment of the septum, starting slightly earlier on the left, (2) simultaneous depolarization of much of the right and left ventricular walls, (3) late activation of the basal septum and the posterior wall and the tips of the papillary muscles. In the normal dog heart the entire process takes about 35 msec.

In LBBB both the pattern of spread and the total time of activation are markedly altered, as seen in Fig. 4,*A*, bottom. As in the control, the heart is cut into 4 planes paralleling the base. The drawing represents a single experi-

ment utilizing more than 40 electrode insertions and over 500 separate recording points. The findings in 8 other experiments, some of which were equally extensive, agree completely with those presented. The earliest activity, occurring a few milliseconds before the onset of the QRS, is seen in Plane III at the anterior border of the right cavity. During the first 15 msec. of the QRS, depolarization

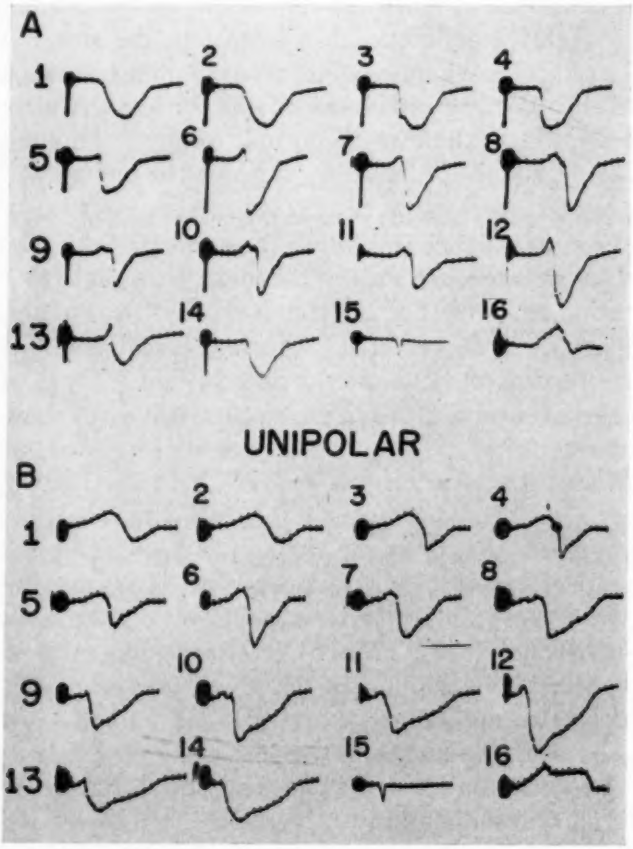

Fig. 1.—Unipolar septal potentials before and after LBBB. Negative potentials are downward. Time pips are 5 msec. apart. Potentials from left cavity on Channels 1 and 2, from septum on Channels 3 through 13, and from right cavity on Channel 14. Channels 15 and 16 record fixed time-reference potential and Lead II ECG, respectively. *A*, Potentials during normal excitation. *B*, After LBBB, same electrode. This electrode was in the position of the septal arrow in Fig. 4,*C*.

occurred in tissues normally activated by the right bundle, i.e., the right septal and ventricular myocardium. Depolarized muscle formed a conelike structure on the right side of the heart, extending into all 4 planes. During the first 15 msec. there was no depolarization of septal tissue normally activated from the left side.

For the next 30 msec. the wave front progressed in an orderly manner across the septum from right to left, roughly paralleling the curvature of the septum. The earliest activation on the left septal endocardium is seen posteriorly in Plane IV. This area became excited early in the interval between 30 and 45 msec.

after the onset of QRS. Within the 30-to-45-msec. period small areas on the anterior left septal endocardium, at the level of Planes II and IV became excited, followed early in the 45-to-60-msec. period by similar areas in Planes I and III.

While parts of the left septal endocardium were not yet activated during the period from 45 to 60 msec. after the beginning of the QRS, ventricular excitation extended to the anterior and posterior epicardial surfaces in all planes, reaching posterolaterally in Plane I. One of the earliest points on the left to be excited appears on the septal portion of the anterior epicardium at about the level of Plane I. During this 45-to-60-msec. period, depolarization of the anterior and posterior walls was nearly completed, with a ring of activated tissue appearing in Plane I. This activated muscle extended into Planes II, III, and IV as a continuous sheet. During a few milliseconds of this period a wide area of the anterior endocardium in Plane IV became activated.

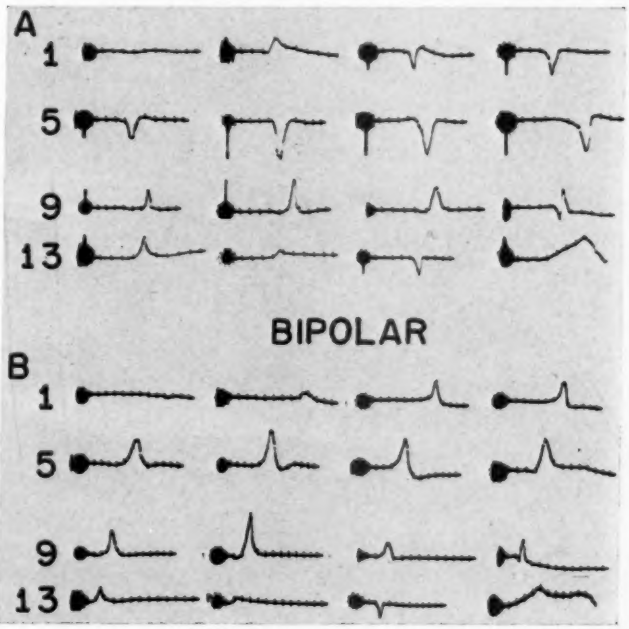

Fig. 2.—Bipolar septal potentials (difference between adjacent tips) before and after LBBB. Records from the same electrode insertion as Fig. 1. Upper potentials (*A*) during normal excitation. Lower records (*B*) after LBBB. Channels 3 through 8 show negative deflection in the normals, indicating activation from electrode tip to base (i.e., left to right). After block the potentials become positive on these channels, indicating activation from the right. Potentials on Channels 9 through 13 are positive normally. After block these channels show no change compared to the normal. Channels 2 and 14 are near the endocardium in the right and left cavities, respectively. Discussion in text. Channels are numbered as in Fig. 1.

Within the 60-to-75-msec. period activation in Plane I was completed. In the other 3 planes the remaining left endocardium became completely activated, suggesting spread by the Purkinje network. Most of the left lateral myocardium was excited during this period. The papillary muscles and extreme lateral myocardium remained to be excited. In the subsequent 15 msec. most of these

areas became activated, depolarization being completed in Plane II. The remaining tissues (a small segment on the left lateral wall in Planes III and IV, and a tip of the anterior papillary muscle in Plane III) were activated in the next 10 msec., to complete the process approximately 100 msec. after the onset of the QRS.

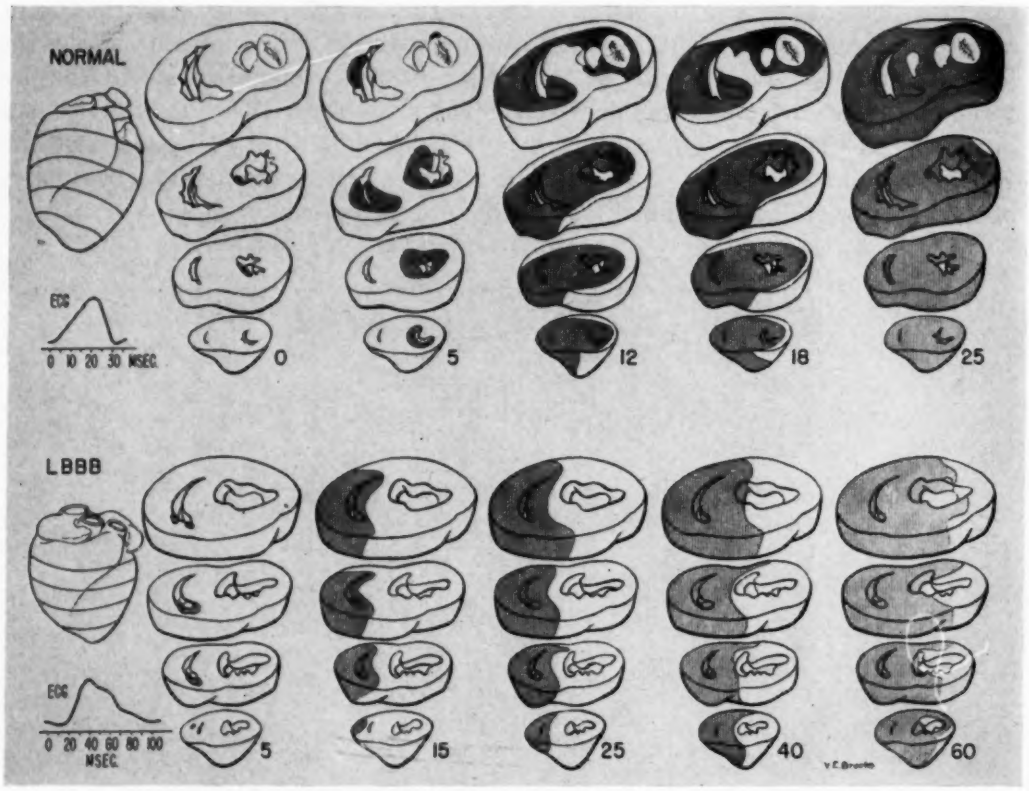

Fig. 3.—Summary of ventricular depolarization patterns before and after LBBB. Shaded area represents volume of myocardium depolarized up to the particular instant indicated by the figures in the columns. These figures represent time in milliseconds after the beginning of QRS. Both the normal and LBBB patterns are referred to the respective Lead II electrocardiograms shown on the lower left of each series of drawings. Normally, depolarization is almost entirely complete by 25 msec. After LBBB the altered mechanism of excitation accounts for the prolonged depolarization. Discussion in text.

Several significant points are not clearly apparent in Fig. 4,*A*. First, since the wave front is concave as viewed from the left, activity occurs at some left epicardial points before it reaches the underlying endocardium. As previously noted, the earliest activity on the left is intraseptal and epicardial after LBBB. Second, a transition occurs following septal activation. Fig. 4,*C* shows this transition, the arrows indicating the direction of spread and amount of tissue activated by the advancing wave front. With the early activation of the left epicardium, outside-in spread occurs. In time, the left septal endocardium is excited and the wave front spreads endocardially, and depolarization commences

on the free wall bordering the cavity. Finally, as the wave front moves laterally, the impulse appears to enter the endocardial conduction network, initiating endo-epicardial spread.

Fig. 3, bottom, summarizes depolarization in the canine heart following LBBB. Earliest ventricular excitation occurs in the tissue surrounding the anterior border of the right ventricular cavity. Fifteen milliseconds after the onset of the QRS there is depolarization of tissue activated by the right bundle, i.e., the right septal and ventricular myocardium. The wave front advances

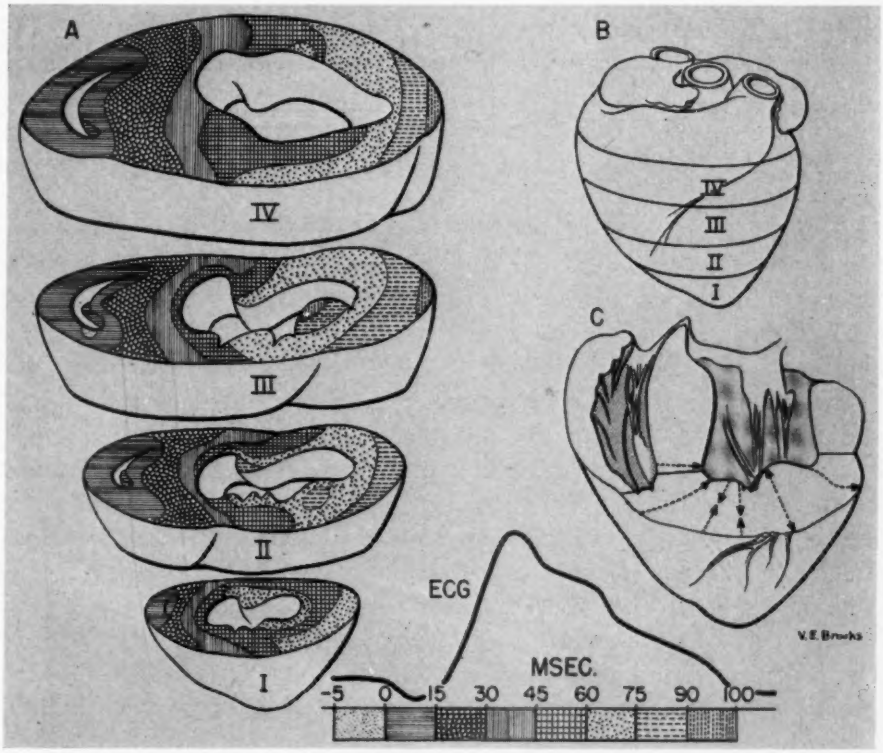

Fig. 4.—Ventricular excitation pattern after LBBB. *A*, **A heart cut by 4 planes parallel to base.** *B*, **Various shadings delineate areas excited at particular intervals during ventricular depolarization. Except for earliest and latest areas each shading represents a 15-msec. period. See scale below Lead II ECG for reference.** *C*, **Shows the pattern of depolarization at the junction of septum and left wall. At the anterior septal region there is epi-endocardial spread. As the wave moves to the left there is epi-endocardial spread from both endocardium and epicardium toward the center of the wall. At the lateral wall endo-epicardial activation is present. Arrows represent the direction of spread and amount of tissue activated by the advancing wave front. Details in text.**

transseptally right to left, in orderly fashion. In contrast to activation of the intact heart where excitation is complete in 35 msec., septal depolarization is still going on at 40 msec. after LBBB. By this time the anterior and posterior epicardium has become activated. At 60 msec. after the onset of QRS, the septum and most of the anterior and posterior walls are activated, leaving the lateral wall and papillary muscles to be excited.

DISCUSSION

Septal Activation in LBBB.—Lewis[1] described the left ventricular conduction tissue as fanning out from the main left bundle and running from the septum to the bases of the papillary muscles. In LBBB this main bundle is interrupted and the septum is activated entirely from the right—single envelopment as opposed to normal double envelopment. Initial activation of the left ventricular myocardium is entirely from the right, and is completely independent of any branches of the main left bundle.

In nearly 50 septal insertions, the wave of excitation advanced across the septum at a uniform rate with no evidence of intraseptal delay as has been postulated.[12-14] These findings concur with previous reports[11] that alteration of septal activation in LBBB accounts for the major portion of the QRS prolongation.

The QRS complex in a normal Lead II canine electrocardiogram lasts 30 to 40 msec., but after LBBB this complex lasts as long as 100 msec. Over half of this time, i.e., 50 to 60 msec., is needed for septal activation by single envelopment.

Activation of the Free Wall.—While some workers[12-14] believe that ventricular mural excitation proceeds in normal fashion following LBBB, others[11] have found changes in the spread through the left ventricle. Our experiments reveal an abnormal pattern of depolarization in the free left wall after LBBB.

The mural phase of ventricular depolarization is lengthened as a result of these conduction and excitation changes in the blocked ventricle. Normal myocardial activation requires 30 to 40 msec. When this period is added to the time required for septal activation in LBBB, 10 to 20 msec. remain unaccounted for. Alterations in (1) rate of conduction, (2) site of early activation, (3) direction of spread, and (4) sequence of depolarization account for this time difference. These changes can be seen by comparing the patterns of activation before and after LBBB (Fig. 3).

Normally, the left endocardium is excited early and almost simultaneously. After LBBB, recordings from both endocardium and epicardium reveal that a small area on the anterior left epicardium is excited before any of the left endocardium. The wave of excitation advances by muscle conduction through the medial half of the left ventricle. The interval between the earliest and latest points is increased after LBBB. The altered pattern of spread after block is shown by arrows in Fig. 4. The anatomic arrangement (spiral) of the apical musculature may account for the epi-endocardial spread on the left.

Canine studies[18] reveal that an anterior myocardial infarction is difficult to determine in the presence of LBBB. Recently, Grant[19] reported that some anterior myocardial infarctions produce QRS prolongation resembling that caused by LBBB. He offers limited criteria for differentiating the two entities, but does not explain why they result in similar electrocardiographic patterns. The epi-endocardial spread of activation noted at the junction of the septum and the left free wall (Fig. 4) is one probable reason for the difficulty in differentiating and diagnosing myocardial infarction and LBBB.

Cavity Potentials.—Several workers have noted that following LBBB the initial intracavity potential on the homolateral side is positive instead of nega-

tive. Normally, the left cavity potentials show only negativity, but after LBBB an initial positive potential, lasting 40 msec., precedes the negative deflection. The positive deflection indicates right-to-left septal activation, and the following negative deflection reflects later activity receding through the left wall. Right cavity potentials show the converse change. While a positive deflection normally precedes a large negative potential, only negativity is seen after LBBB. Septal potential changes, from negative to positive, strengthen the conclusion reached from cavity records[7-10] that septal activation spreads from right to left after LBBB.

QRS Complex.—The QRS complex in a Lead II electrocardiogram is prolonged after LBBB. The new sequence of depolarization, caused by alterations of the septal and mural phases of activation, accounts for the changes in this complex. Depolarization of the septal tissue normally activated from the right end of the right free wall produces the initial (negative) deflection, lasting about 15 msec. After a rapid positive deflection due to activation of most of the septum, a plateau appears in the complex. This plateau persists as the remaining septal tissue, much of the apical region, and the anterior and posterior myocardium are activated. In the last 40 msec., the remaining free wall is excited, as the QRS complex returns to the base line.

Wilson and his co-workers[20] compared direct (epicardial) and precordial leads in dogs with conduction defects, and found marked similarity in the QRS complexes. Also, the precordial electrocardiograms obtained in canine bundle branch block were not essentially different from those obtained in human bundle branch block. Comparison of bipolar limb leads from Wilson's work[21] with those taken during these experiments revealed no significant difference. This finding further supports the concept that canine and human electrocardiograms are similar, and justifies the interpretation of experimental work on dogs in terms of human electrocardiography.

SUMMARY

The pattern and mechanism of ventricular excitation following experimental left bundle branch block was studied in detail by means of a multichannel recording system.

After interruption of the main left bundle, the septum is activated from right to left. This depolarization proceeds in orderly fashion with no evidence of intraseptal delay. Single rather than double envelopment of the septum accounts for the septal phases of the prolonged QRS complex. This type of septal activation accounts for more than half the duration of the QRS after LBBB.

Mural activation on the blocked side occurs first on the anterior epicardium. The excitation wave apparently reaches this region by muscle conduction across the septum. Initially there is epi-endocardial spread in this region of the mural myocardium. Such a pattern of spread may be one reason why differentiating LBBB and anterior myocardial infarction is sometimes difficult. As the excitation wave proceeds laterally, its direction of spread becomes endo-epicardial.

Changes in (1) the earliest activated site, (2) the rate of conduction, (3) the direction of spread, and (4) the sequence of depolarization in the left ventricular wall also contribute to the prolongation of the QRS.

The inscription of the QRS complex in a Lead II electrocardiogram is correlated with the order of depolarization. Records from bipolar limb leads further substantiate the similarity between human and canine electrocardiograms.

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The Vectorcardiogram of Ventricular Activation in Chronic Coronary Heart Disease

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Abnormalities of the QRS complex due to intraventricular conduction defects or to some other cause are frequent findings in chronic coronary heart disease (CCHD). Sometimes they follow a definite pattern, as in right[1,3,9] or left[12,22] bundle branch block; some others are ill defined, as in left ventricular enlargement or myocardial fibrosis. Even in bundle branch block certain QRS abnormalities are not easily attributable to the block itself.[5] Therefore, in this paper we attempt to analyze the different vectorcardiographic patterns and discuss their mechanism of production.

MATERIAL AND METHOD

The present paper includes clinical, electrocardiographic, and vectorcardiographic studies in a series of 34 patients with CCHD. All cases were collected from the Instituto Nacional de Cardiología de México. Three main groups were considered, according to their electrocardiographic and vectorcardiographic behavior: Group A (11 cases), Group B (10 cases), and Group C (13 cases). We also include the tracings of 6 normal subjects, who were more than 40 years of age, as a graphic control of the initial vectors in the horizontal VCG.

The electrocardiographic study includes standard and unipolar limb leads, as well as 6 precordial leads. For the recording of the VCG, we used Grishman's "cube" method,[8] kept the interelectrode distances strictly equal, and placed the cube in such a way that a horizontal plane passing through the fourth intercostal space divided the cube into 2 equal parts. We consider that this procedure is recommendable for greater accuracy of the cube method.

In every case, frontal and horizontal simultaneous VCG curves were obtained with low and high amplification (1 mv. = 1 inch and 1 mv. = 3 inches), and with 200 and 500 per second spot interruptions. We consider these technical requirements as strictly indispensable for the identification of the initial and slurred portions of the loops (Fig. 1).

The age of our patients ranged from 40 to 94 years (Table I), with an average of 60 years. Only one patient, with coronary insufficiency of unknown etiology, was under 40 years of age. All cases had atherosclerotic or hypertensive heart disease except Case 10 in whom a double aortic lesion of rheumatic origin was present. Nineteen of our cases were men and 15 women, averaging 63 and 54 years, respectively.

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TABLE I

CASE	REGISTRATION NUMBER	AGE (YEARS)	SEX	QRS DURATION (SEC.)	BLOOD PRESSURE (MM. Hg)	PULMONARY EMPHYSEMA	CHRONIC COR PULMONALE	ANGINA PECTORIS
1	51620	53	F	0.16	170/100			
2	52411	60	F	0.13	130/80	+	+	+
3	51084	63	M	0.14	160/85			+
4	48512	60	F	0.16	160/85			+
5	52224	65	M	0.14	210/110	+		
6	48234	56	F	0.18	175/100	+		
7	51897	56	M	0.14	170/100	+		+
8	52410	78	M	0.10	130/80	+		+
9	45833	63	F	0.09	190/100	+		
10	43723	40	F	0.08	140/90*			
11	51050	24	M	0.11	†			
12	52276	62	M	0.13	190/110			
13	51437	94	M	0.12	160/90	+	+	
14	51349	68	M	0.13	250/125			+
15	51456	73	M	0.12	170/70	+		
16	52161	65	F	0.12	230/110	+		
17	Private Case	68	M	0.13	160/90			
18	50917	79	M	0.13	220/110	+	+	
19	51964	63	M	0.13	125/75			+
20	43778	45	F	0.09	218/108			
21	48591	56	M	0.09	140/70	+	+	
22	24624	55	M	0.08	175/100			
23	50897	56	F	0.08	180/100	+		
24	49650	50	F	0.06	190/120	+		+
25	51099	45	F	0.07	240/130			
26	50007	57	F	0.08	150/110	+		
27	50711	66	M	0.08	220/130			
28	51749	56	M	0.08	150/90	+		
29	51305	53	F	0.07	260/156	+		
30	46706	63	F	0.07	140/70			
31	38004	56	M	0.08	210/160			
32	44708	58	M	0.08	270/140	+		+
33	52147	70	M	0.07	190/140	+		
34	45231	56	F	0.06	160/90			+

*Aortic stenosis and regurgitation.
†Left heart failure of unknown etiology.

RESULTS

Group A.—This group includes 11 cases (Fig. 2) without evidence of myocardial infarction where the QRS_H loop showed a clockwise rotation. We shall refer to them as cases of left bundle branch block (LBBB); they are classified as either "complete" (Cases 1 to 7) or "incomplete" (Cases 8 to 11), according to duration of the QRS loop above or below 0.12 second. Angina pectoris was a frequent finding here (5 cases). A systemic diastolic pressure of 90 to 100 mm. Hg was found in 4 cases; higher diastolic figures were found in only 1 case.

The initial part of the QRS loop (Q loop) was always abnormal in this group (Fig. 3): in all cases but one (Case 3) it started anteriorly and to the left, instead of being anterior and to the right; it usually made a sharp bend before turning backward (Cases 1, 2, 4, 5, 6, 8, 11). The speed of inscription of the Q loop in "complete" block, was often slow, while in "incomplete" block it was normal.

The QRS loop of the horizontal plane was always directed posteriorly and to the left (Table I, and Figs. 2 and 4) with a clockwise rotation. The J point was displaced anteriorly and to the right (+130° to +165°; mean value +151°), especially in hypertensive patients. The speed of inscription was fast at the centrifugal limb (except in Cases 6 and 10) and slow during the early segment of the centripetal limb as well as at the junction of both limbs (except in Case 3). This junction or intermediate plateau was often the seat of irregularities which were found to be proportional to the slowness of inscription; only 2 cases showed a tiny counterclockwise loop at the intermediate plateau.

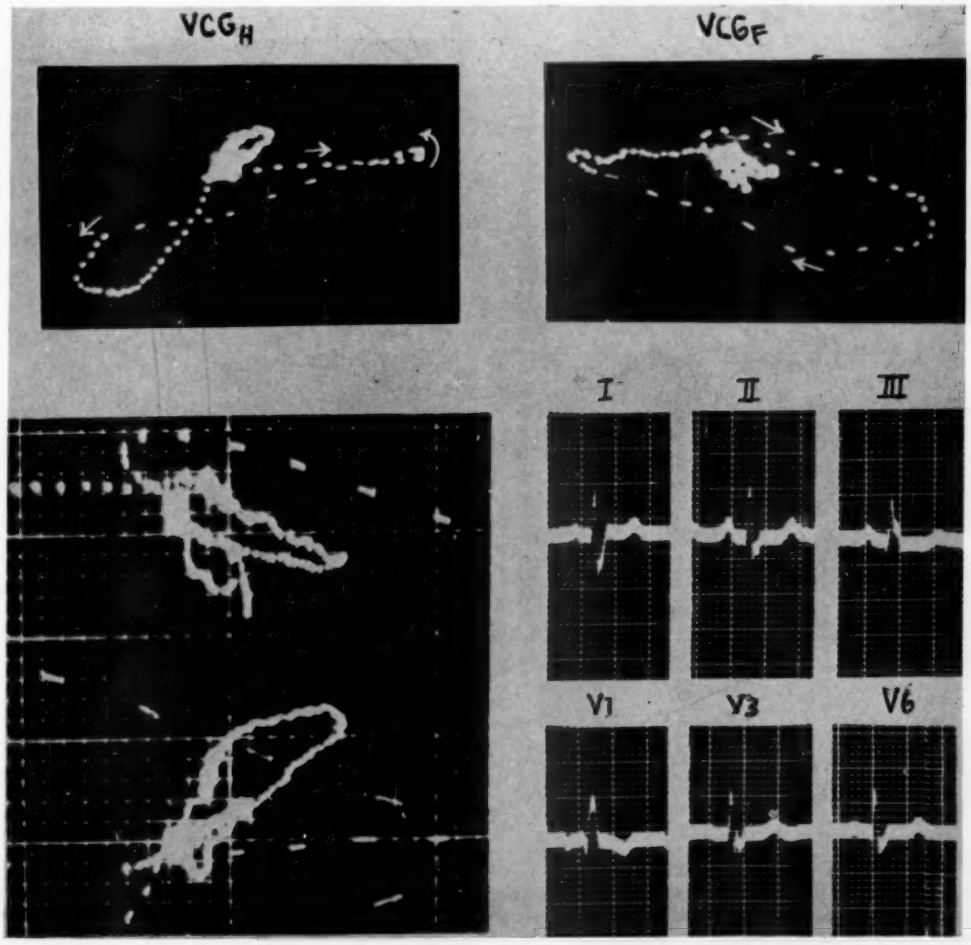


Fig. 1.—ECG and VCG in a case with right bundle branch block and chronic coronary insufficiency. The initial vectors cannot be identified in the horizontal VCG, even with a high amplification. Nevertheless, the Q loop can be recognized when the horizontal and frontal VCG are taken simultaneously, as in the lower part of the figure.

The QRS$_F$ loop had a counterclockwise rotation (Fig. 4), except in Cases 8 and 10 which showed a figure-of-eight loop. There were 2 slurrings of the QRS$_F$ loop, both corresponding to those found in the horizontal plane: one at the beginning of the centrifugal limb and the other at the intermediate junction.

The extension of these slurrings was greater in the frontal than in the horizontal plane, i.e., the initial slurring was artificially prolonged in the frontal plane because the centrifugal limb was directed posteriorly and almost perpendicularly to this plane; the intermediate plateau also appeared exaggerated in the same plane because of its forward orientation.

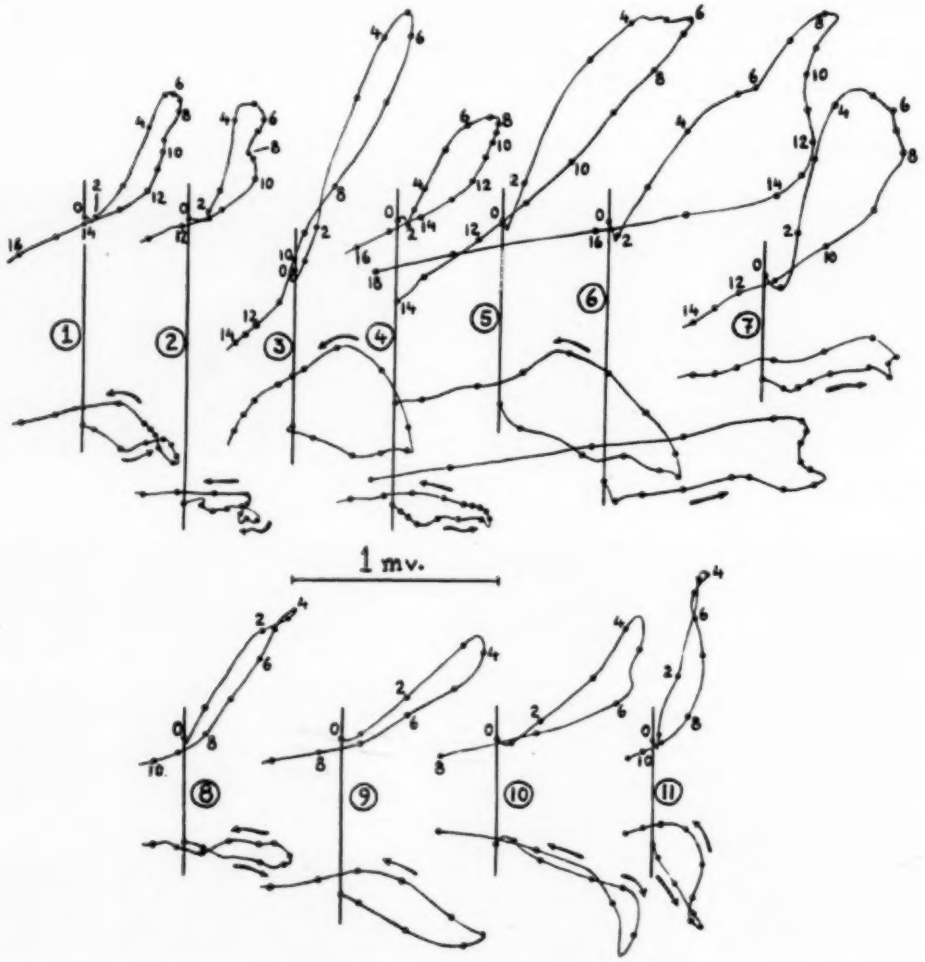


Fig. 2.—The QRS loop of 11 patients with left bundle branch block: the last 4 cases correspond to incomplete LBBB. In each case, the upper tracing represents the horizontal and the lower tracing the frontal QRS loop. Notice a clockwise rotation of the QRS_H loop with a counterclockwise rotation of QRS_F. An intermediate slurring is usually present in both planes. The centrifugal limb of the QRS loop is not slurred in the horizontal plane but, sometimes, it is artificially slurred in the frontal plane.

Group B.—This group (Fig. 5) includes 10 cases (12 to 21) whose electrocardiograms presented an rsR′ or qR complex in V_1 with a definite slurring or small plateau of the R wave. They were considered as typical instances of right bundle branch block (RBBB). Eight of them had a QRS duration of 0.12 second or more ("complete" blocks), while Cases 20 and 21 had a duration of less than 0.12 second ("incomplete" blocks).

A systemic diastolic hypertension was found in 7 cases of Group B, 5 with severe and 2 with mild hypertension. Angina pectoris was observed in 2 cases; pulmonary emphysema in 4, and chronic cor pulmonale in 1 case.

The initial loop may be considered within normal limits in Cases 18 and 19. In all the other cases the initial loop was absent or too small (Fig. 3). However, a sharp bending similar to that of Group A was never seen, and a marked slurring of the Q loop was rare (Cases 14, 15, and 19). Besides the Q loop, we have to distinguish 2 main segments which we call the R and S loops (Figs. 5 and 6). The R_H loop had a uniform inscription and was directed to the left, either posteriorly or anteriorly. Its voltage (Table II) and its backward orientation were less important than in Groups A and C. The total voltage of the R loop was greater in cases with severe hypertension (Table III). This loop usually had a clockwise rotation in the horizontal plane (Cases 13, 14, 15, 17, 18, and 21), sometimes a counterclockwise rotation (Cases 19 and 20), or a figure-of-eight configuration (Cases 12 and 16), while the R loop in the frontal plane may have a counterclockwise or clockwise rotation (Fig. 6).

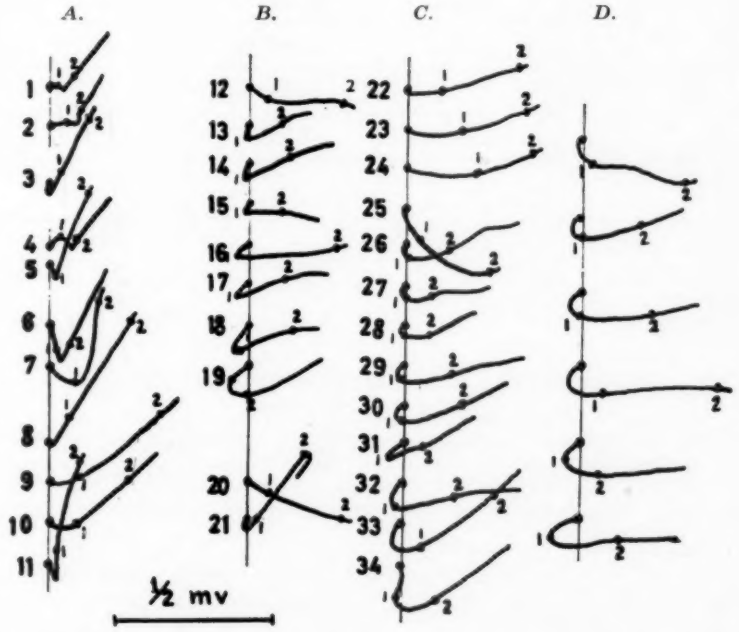


Fig. 3.—The initial vectors of the horizontal QRS loop in 34 patients with chronic coronary insufficiency (*A*, *B*, *C*) as well as in 6 normal patients (*D*). Notice that Group *A* presents important abnormalities, while Groups *B* and *C* have only minor changes. Notice also the morphologic similarities between Groups *B* and *C*.

The S loop was always oriented anteriorly and to the right, with a counterclockwise rotation in the horizontal plane. Its total voltage was greater in emphysematous patients (Table III). The intermediate portions of the S loop were slurred and irregular, but its final portion was always rapid and smooth, ending with a backward displacement of the J point. In the frontal plane, the last limb of the S loop was slurred all along, but only the initial segment of this

limb had a definite slurring in the space; its last segment was artificially slurred because it moved almost perpendicularly to the frontal plane.

TABLE II

				LIMITS	MEAN VALUE
Group A	ÂQRS			+85° to −45°	+12°
	Maximum Vector		α	+35° to −10°	+13°
			β	−66° to −35°	−51°
Group B	ÂQRS	First part*		+75° to −30°	+18.5°
		Second part†		+175° to −150°	−176.5°
	Maximum Vector	α	R loop	+47° to −58°	+11°
			S loop	+161° to −145°	−176°
		β	R loop	+12° to −48°	−5°
			S loop	+114° to +146°	+127°
Group C	ÂQRS			+50° to −60°	−1.15°
	Maximum Vector		α	+36° to −8°	+13°
			β	−45° to −8°	−25.69°

*Corresponds to R loop.
†Corresponds to S loop.
α = Frontal plane.
β = Horizontal plane.

TABLE III. VOLTAGE OF SPATIAL MAXIMUM INSTANTANEOUS VECTORS IN VARIOUS CLINICAL CONDITIONS

GROUP		HYPERTENSION			PULMONARY EMPHYSEMA		
		SEVERE	MILD OR ABSENT	TOTAL	WITH	WITHOUT	TOTAL
A		1.212*† (2)	1.142 (9)	1.154 (11)	1.107 (7)	1.238 (4)	1.154 (11)
B	R loop	0.575 (5)	0.346 (5)	0.461 (10)			
	S loop	0.524 (5)	0.736 (5)	0.630 (10)	0.793 (6)	0.386 (4)	0.630 (10)
C		0.921 (7)	0.479 (6)	0.718 (13)			

*Of doubtful statistical value.
†Values are given in millivolts.
Figures in parentheses indicate number of cases.

Group C.—This group includes 13 cases (22 to 34) with a QRS duration of less than 0.12 second (Fig. 7). The ECG tracings of this group were classified as "incomplete left bundle branch block" of first or second degree, because they showed absence or reduction of the Q wave and initial slurring of the QRS complex in the "left epicardial" leads. However, the QRS loop presented a counterclockwise rotation in the horizontal plane. Arterial hypertension was present in 12 out of these 13 cases (8 with severe and 4 with mild diastolic hypertension); angina pectoris was present in 3 instances, pulmonary emphysema in 7, and chronic cor pulmonale in none.

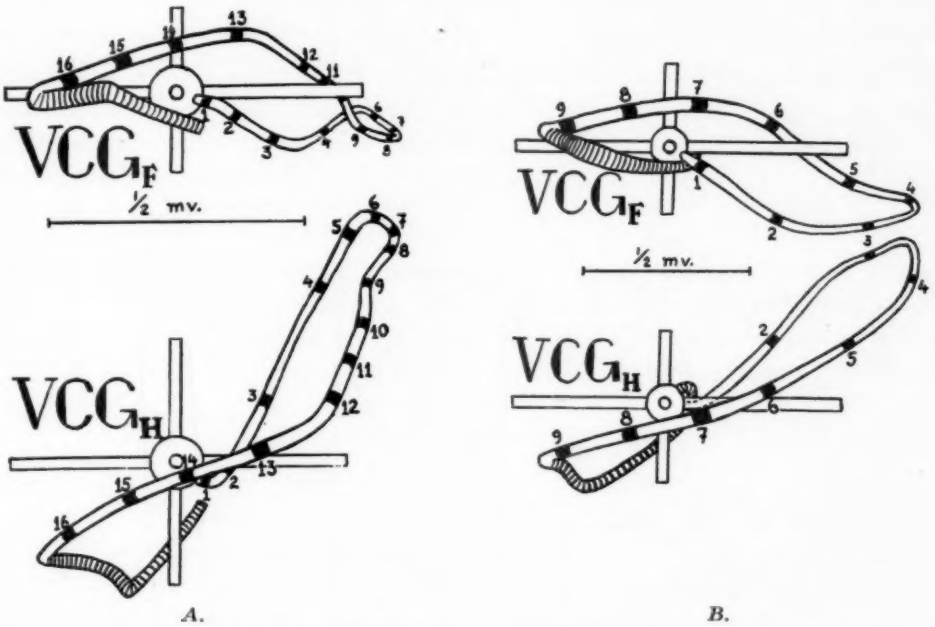


Fig. 4.—*A*, Spatial VCG in a patient (Case 1) with complete LBBB. VCG_F = frontal view; VCG_H = upper view. Notice an irregular contour and definite slurring of the intermediate portion of the R loop, a low voltage with abnormal orientation of the Q loop, and a clockwise rotation of the QRS_H loop. *B*, Spatial VCG in a patient (Case 9) with incomplete LBBB and moderate arterial hypertension. Notice the abnormal Q loop with clockwise rotation of QRS_H and absence of an intermediate slurring.

The behavior of the initial loop was always abnormal (except in Case 33) and was similar in every respect to that of Group B (Fig. 3). Most of the time the Q loop was absent (Cases 22 to 25) or too small (Cases 26 to 31). At other times the Q_H loop was apparently normal, but the Q_F loop presented an upward start with counterclockwise rotation of the VCG_F (Case 32) or it had a marked twisting which went out of the general plane of the spatial VCG (Case 34). Let us point out that, except in Cases 27 and 28, there was not an abnormal slurring of the Q loop in the space, although the forward direction of its onset gave rise to an artificial reduction and slurring in the frontal plane (Cases 25, 29, 30, 33, and 34).

The mean direction of the QRS loop was to the left and slightly backward and downward (Figs. 7 and 8; Table II). A counterclockwise rotation of the QRS loop, in both the horizontal and frontal planes, was a very constant finding.

The total voltage of the R loop tends to be proportional to the blood pressure figures (Table III). The speed of inscription of the QRS loop was uniform, similar to that of normal subjects, without an intermediate plateau in any case. Nevertheless, a few cases showed a faint slurring at the junction between the centrifugal and centripetal limbs. This slurring had no relation with the Q-loop abnormalities or the total QRS duration. As a rule, the QRS_F loop was narrower and more irregular than the QRS_H loop, because the spatial VCG tends to be parallel to the horizontal plane. The J point was always displaced anteriorly and to the right of the origin.

DISCUSSION

Our findings will be discussed separately for the three groups, giving special attention to their diagnostic value and possible electrophysiologic importance.

Group A, or LBBB.—All the patients of this group (except Case 9) had a Q loop which was oriented anteriorly and to the left. Therefore, in cases of LBBB,

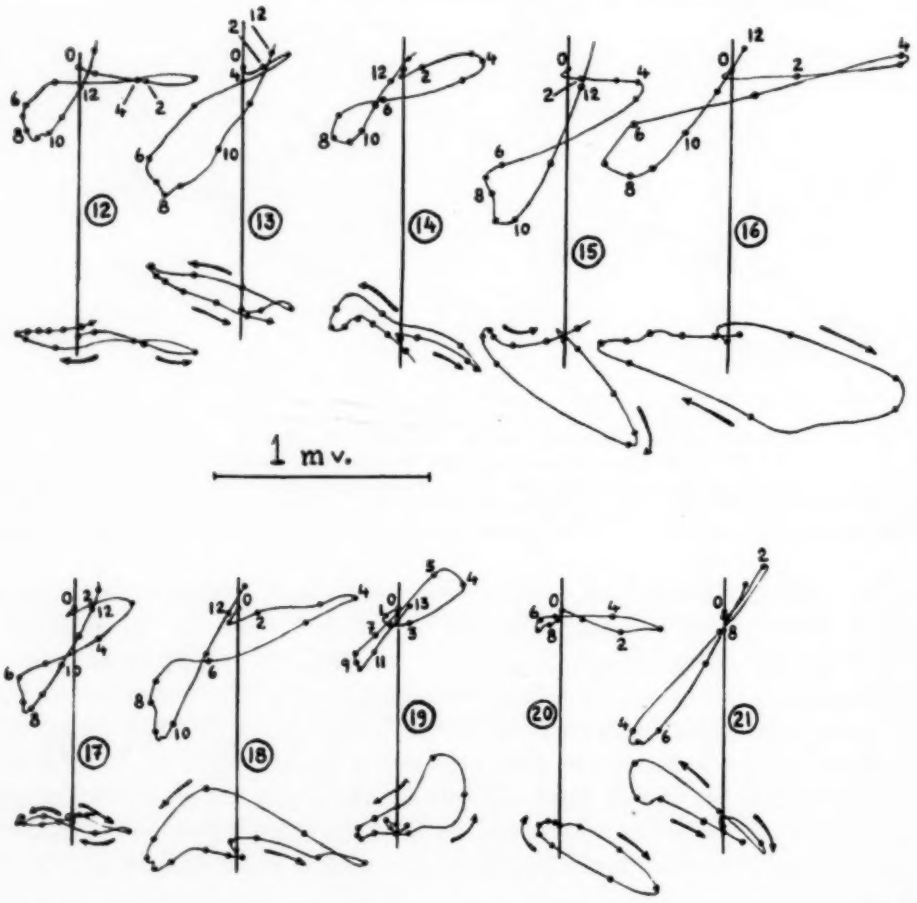
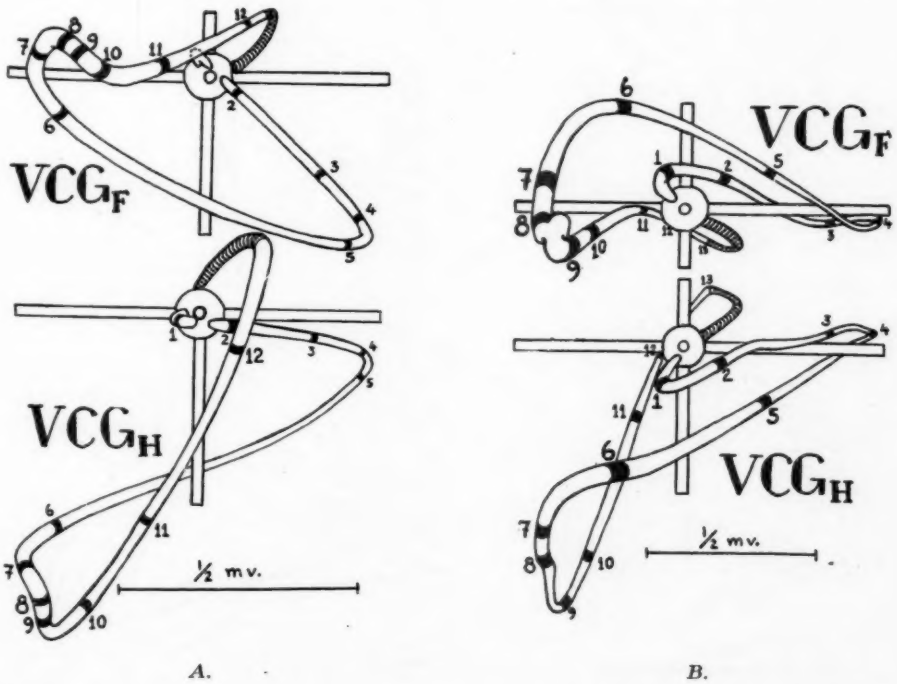


Fig. 5.—The QRS loop of 10 patients with right bundle branch block. The last two cases correspond to incomplete RBBB. Horizontal and frontal QRS loops as in Fig. 2. Notice a preterminal slurring and counterclockwise rotation of the S_H loop in all cases, with an artificial terminal slurring of the S_F loop in some cases.

a small Q wave in the left posterior or left superior leads is not by itself a sign of septal myocardial infarction,[4] although its diagnostic value increases as the exploring electrode moves anteriorly or inferiorly from V_3 or V_L to V_6. On the other hand, ventricular complexes of the QS or qrS type may be found in the right precordial leads of patients with noncomplicated LBBB.[16]

The intermediate plateau of the QRS loop is a very frequent finding in complete LBBB,[6,21] but its electrocardiographic expression in L_1, V_L or V_6 is artificially exaggerated by the forward direction of such a plateau in the spatial VCG. The last portion of the centripetal limb, being rapid and straight, may give rise to a terminal slurring of the S wave in V_3 or V_4, because of reciprocal perpendicularity. Such slurring, less than 0.05 second, would not be a sign of myocardial infarction.[4] The clockwise rotation of the QRS_H loop manifests itself by a sudden delay of the intrinsicoid deflection and a sudden change from the rS type complexes of the right precordial leads to the late R waves (rSr′, rSR′, rsR′) of the transitional leads. Another consequence of the clockwise rotation is the progressive anticipation of the R′ vertex (intrinsicoid deflection) as the exploring electrode moves farther to the left.

Group B, or RBBB.—The absence of a Q loop was found only in Cases 12 and 20, so that the absence of an initial R wave in the right precordial leads of a case with RBBB should arouse suspicion of anteroseptal myocardial infarction[23] or right atrial dilatation.[17] Nevertheless, an upward orientation of the Q_F loop



A. *B.*

Fig. 6.—*A*, Spatial VCG in a patient (Case 15) with right bundle branch block, pulmonary emphysema, and normal blood pressure. Notice a clockwise rotation of the QRS_F loop with "ascending" crossing of the S_H loop. *B*, Spatial VCG in a patient (Case 18) with right bundle branch block, severe systemic hypertension, and mild pulmonary emphysema. Notice a counterclockwise rotation of the QRS_F loop and a "descending" crossing of the S_H loop, indicating a left ventricular hypertrophy.

was found in Cases 12, 14, 17, 18, and 21, giving rise to a deep Q_3 which should not be mistaken for a sign of myocardial infarction. The total voltage of the R loop was proportional to the systemic blood pressure, so that one may expect a high R wave in the "left epicardial leads" of hypertensive patients with RBBB.

The two limbs of the S_H loop always made a crossing. The first limb was either below—clockwise rotation of QRS_F (Fig. 6,*A*)—or above—counterclockwise rotation of QRS_F (Fig. 6,*B*)—the second limb. In both instances, the second

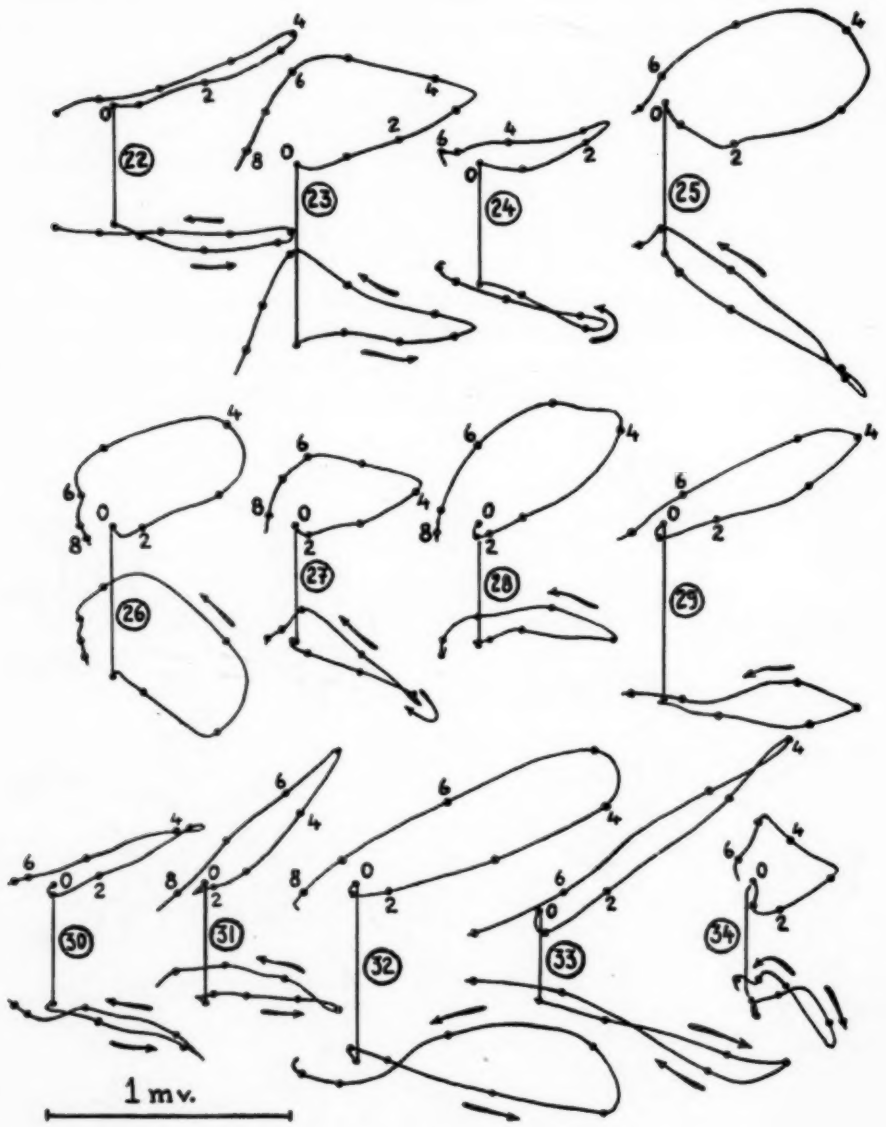
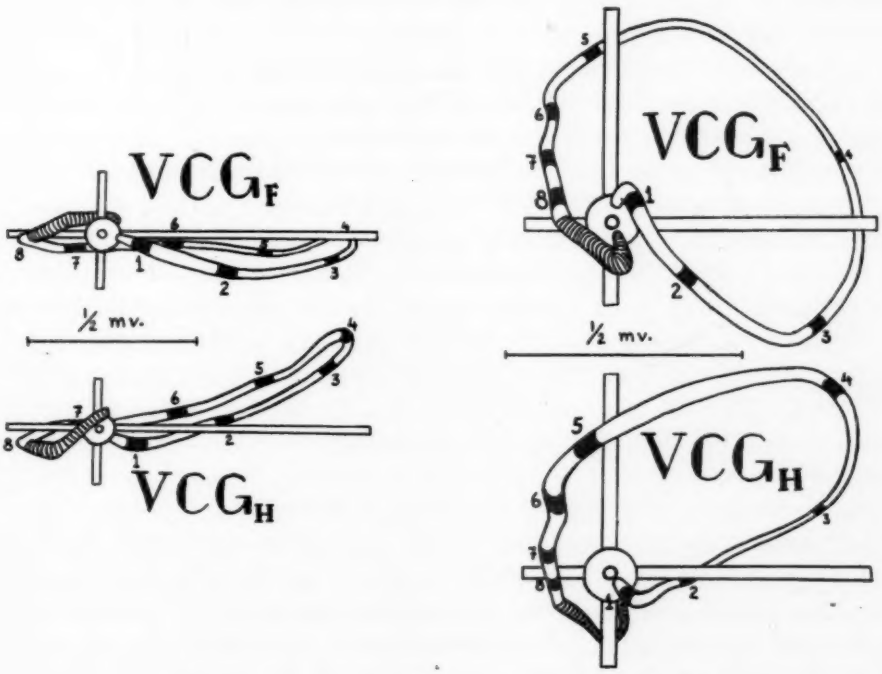


Fig. 7.—The QRS loop of 13 patients with chronic coronary heart disease, electrocardiographic signs of incomplete LBBB, and a counterclockwise rotation of the QRS loop in the horizontal plane. The horizontal and frontal QRS loops as in Figs. 2 and 5. Some abnormality of the Q loop is always present, but a definite intermediate slurring of the R loop is absent.

limb of the S loop moved horizontally while the first limb was variable, i.e., the 2 types of behavior correspond to 2 different figures in the space and it is impossible to reproduce one from the other by means of a mere spatial orientation. Now, inasmuch as a counterclockwise rotation of the QRS_F loop (with or without RBBB) may be a sign of left ventricular enlargement,[9] our observations indicate that intrinsic electrical changes of the heart, not merely heart position, are responsible for such an electrical sign.

The most constant feature of RBBB in CCHD was the forward and rightward orientation of the S loop as well as its counterclockwise rotation and preterminal slurring in the horizontal plane. We must emphasize that although the QRS_F loop may show a terminal slurring, only the spatial loop had a preterminal slurring. This finding supports Vastesaeger's[21] observations rather than Grishman's[3,9] and was to be expected from the experimental point of view. In fact, the severing of the right bundle branch gives rise to a delay in the activation process but without altering its sequence in the free walls of the right ventricle.[11] Therefore, a normal speed of inscription at the terminal portions of the QRS loop was to be expected.

We are aware of the fact that some intraventricular conduction defects, classified as instances of RBBB from both the ECG and VCG points of view[9,6,22]



A. *B.*

Fig. 8.—*A*, Spatial VCG in a patient (Case 22) with moderate arterial hypertension and electrocardiographic signs of incomplete LBBB. The Q loop is absent while the QRS loop has a counterclockwise rotation without an intermediate slurring. *B*, Spatial VCG in a patient (Case 26) with severe arterial hypertension, some pulmonary emphysema, and electrocardiographic signs of incomplete LBBB. The Q loop has almost disappeared, the intermediate slurring of the R loop is absent, and the QRS_H loop has a counterclockwise rotation.

may show a terminal slurring in the spatial VCG. Such cases are in certain respects similar to the so-called "S_1-S_2-S_3" type and may occur in coronary heart disease as well as in rheumatic, congenital, or even normal hearts. This brings up two questions: (1) Should we consider that only preterminal slurrings correspond to RBBB while terminal slurrings are due to focal blocks? (2) If both types correspond to RBBB, how is the sequence of activation responsible for a difference in the VCG behavior and what is the mechanism of those 2 types of activation? At present, we are unable to give an answer to these problems.

As for the Q loop, the influence of a delayed activation in the right bundle branch cannot explain the observed reduction and abnormality of the initial vectors. In fact, transitory RBBB, clinically[1] and experimentally,[13] does not alter the initial deflection of the QRS complex because it does not interfere with a left-to-right normal septal activation. Even more, RBBB enhances the general left-to-right activation of the interventricular septum,[15] so that we might expect an increase, not a reduction, of the initial vectors oriented to the right. On a first approach, one might postulate a superimposed incomplete LBBB, since we are dealing with CCHD where abnormal Q waves and LBBB are frequent findings. Now, a delayed activation of the left septal mass, superimposed on a RBBB might explain the electrical findings. But, if both sides of the human specific system behave as a functional syncytium, as seems to be the case in dogs,[15] there would be few probabilities for a focal LBBB superimposed upon the RBBB.[5] On the other hand, a diffuse delay of activation of the whole left specific system, superimposed upon the RBBB, should merely increase the P-R interval and reduce the importance of the RBBB, without altering the Q loop: an expectation which was not confirmed by ECG observations.[5]

Consequently we arrive at a dilemma: either we suppose that human hearts with chronic coronary insufficiency may give rise to a certain form of "focal" block or we have to consider that some other factor, independent of the RBBB itself and not a superimposed incomplete LBBB, is responsible for the Q-loop abnormality in Group B. This other factor shall be discussed in the next section.

Group C.—In this group, as in Group B, the voltage of the R loop was proportional to the systemic blood pressure, so that in hypertensive patients one may expect a high R wave in Leads I, V_L, V_6 or V_7. The counterclockwise rotation of the QRS_H loop corresponds to a progressive delay and relative preponderance of the precordial R waves as the exploring electrode moves to the left. Absence of the Q wave and initial slurring of R in Leads I, V_L, and V_6 was rarely due to absence of the Q loop (Cases 22-24) or to actual slurring of the centrifugal branch of the QRS loop (Cases 27-28): most cases showed only low voltage of the Q loop (Cases 25-31) and/or a forward orientation of its first limb, with normal speed of inscription. Now, since counterclockwise rotation and upward start of the QRS loop may be present (Cases 23, 26, 28, 31, and 32), a deep Q wave or a QS complex may appear in Leads III or V_F without clinical evidence of myocardial infarction.

Since incomplete LBBB in dogs[15] may preserve a left-to-right septal activation without interseptal* latency, preserving also the upward accession of the

*Let us remember that anatomic[2,10,20] and physiologic[11] studies of the interventricular septum demonstrate the existence of two independent muscular portions, left and right.

free left ventricular wall, one may expect clinical instances of incomplete LBBB with little abnormality of the Q loop, without intermediate plateau of the R loop, preserving the normal counterclockwise rotation of the QRS_H loop. Furthermore, an intracavity R wave of the left ventricle has been found in some clinical cases[14] where the ECG was similar to that of our Group C.

Nevertheless, the possibility of inducing electrical tracings like those of Group C by means of incomplete interruption of the left branch does not demonstrate the reverse: that interruption of the left bundle branch was the only cause or the most frequent cause in tracings like those of our Group C.

Let us remember that abnormalities of the Q loop in Group A, where LBBB is unquestionable, were different from those found in Groups B and C. Since cases of Group A had ECG and VCG curves which were typical of LBBB,[12] including clockwise rotation of QRS_H, presence of intermediate plateau of R, and absence of a past history of myocardial infarction, we may ascribe the Q-loop abnormality and clockwise rotation of their QRS_H loop to abnormal right-to-left septal activation[15] and abnormal base-to-apex accession of the free wall.[19] But in Group C the abnormality of the Q loop, while different from that of Group A, is very similar to that of Group B, where an incomplete left bundle branch block superimposed upon a RBBB seems to be highly improbable. In other words, if a certain factor not related to bundle branch block may induce a Q-loop abnormality in coronary-hypertensive patients with RBBB (Group B), one may expect the same factor to induce similar abnormality with similar statistical incidence in coronary-hypertensive patients without RBBB (Group C). In fact, resemblance between Groups B and C is threefold: (1) morphologic, as far as the Q wave[5] and Q-loop abnormalities are concerned; (2) clinical, because both groups correspond to CCHD, usually with systemic hypertension; and (3) statistical, because in a previous electrocardiographic study[5] of patients with CCHD and counterclockwise rotation of the heart, we found such abnormality of the Q wave in 32 per cent of 50 cases with RBBB, and in 37 per cent of 62 cases without RBBB.

This brings up the following questions: How many of the cases in Group C are true instances of incomplete LBBB, and how many are not? How can we make the diagnosis of incomplete LBBB by means of the ECG or VCG? At present, according to the statistical distribution already mentioned, we are inclined to consider that an important part of our cases in Group C are not true instances of incomplete LBBB. On the other hand, we admit our inability to make a definite diagnosis in a given instance of this group by means of the VCG or the clinical ECG.

Inasmuch as a counterclockwise rotation of the QRS_H loop and the absence of an intermediate plateau are normal findings, while Q-loop abnormalities of Group C were also found in Group B, we consider that the cardiologist should not make the diagnosis of incomplete LBBB in a case with electrical signs of left ventricular enlargement, small or absent Q waves in the "left epicardial leads," and a slight initial slurring of the R wave in such leads, unless an R wave in the left intracavity tracings, or a marked slurring of QRS in the clinical ECG, or a sudden shift to a higher degree of LBBB are found.

As for the nature of the factor which might induce the Q-loop abnormalities in Groups B and C, two hypotheses should be mentioned: (1) an intrinsic reduction of the initial vectors brought out by loss of some muscular units, and (2) a neutralization of the initial vectors brought out by increase of synchronous antagonistic forces. The usual finding of muscular subendocardial fibrosis[7] of the interventricular septum in cases of CCHD speaks in favor of the former hypothesis. On the other hand, hypertrophy of the free left ventricular wall speaks in favor of the second hypothesis, since it increases the voltage of the high posterolateral vectors, these being opposed to and, for a certain time, contemporary* with the left septal vectors. In this respect, let us remember that 7 out of 10 cases in Group B and 12 out of 13 cases in Group C had also arterial hypertension and electrical signs of left ventricular hypertrophy.

SUMMARY AND CONCLUSIONS

The ECG and VCG tracings of 34 patients with chronic coronary heart disease were studied. They were classified in three groups: (A) 11 cases with left bundle branch block (LBBB); (B) 10 cases with right bundle branch block (RBBB); (C) 13 cases with electrocardiographic signs of incomplete LBBB but a counterclockwise rotation of the QRS loop in the horizontal plane.

The conclusions arrived at in this study are as follows:

1. Tracings of Group A are considered as being due to LBBB because they present a clockwise rotation of the QRS_H loop, left posterior orientation of the electrical axis, and an intermediate slurring of the R loop, without a past history of myocardial infarction.

2. Tracings of Group B, classified as RBBB from the ECG and VCG viewpoint, had a characteristic pattern in the horizontal VCG: the S_H loop was always oriented anteriorly and to the right, presenting a counterclockwise rotation regardless of rotation of the R_H loop. A real terminal slurring of the QRS loop was never found: there were a preterminal slurring of the S_H loop and a false terminal slurring of the S_F loop due to the anteroposterior orientation of the VCG.

3. Tracings of Group C, classified as incomplete LBBB from the ECG viewpoint, had a counterclockwise rotation of the QRS_H loop without an intermediate plateau. They showed only minor changes of the Q loop, similar to those of Group B but different from those of Group A. We consider that the majority of these tracings do not correspond to incomplete LBBB but are due to septal myocardial fibrosis and/or left ventricular hypertrophy.

4. It is advisable not to make the diagnosis of incomplete LBBB by the clinical ECG alone, unless there is a marked initial notch of QRS in the "left epicardial leads," an evolution to complete LBBB, a clockwise rotation of the QRS_H loop, or an initial positivity of the QRS complex in the left intraventricular leads.

5. We consider that a rational approach to ECG interpretations should

*Even if left septal activation begins earlier than activation of the free left ventricular wall, most of the subendocardial surface of the former has an activation which is simultaneous with that of the latter.[18]

take into consideration the spatial distribution of heart currents, as they manifest themselves in the spatial VCG, in order to avoid common errors in the diagnosis.

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Depressant Effect of Ether on the Heart: A Study With the Ultralow-Frequency Force Ballistocardiograph

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Toxic effects of ether on the heart have been demonstrated repeatedly in laboratory preparations[1-7]; yet it has been accepted as a fact that ether stimulates the cardiovascular system of man. These apparently conflicting concepts were finally resolved by the discovery that, although ether does have a direct negative inotropic effect on the canine heart, this action is mitigated by the positive inotropic effect of epinephrine and norepinephrine reflexly released during anesthesia.[8] Subsequent measurements on intact dogs with strain-gauge arches on their ventricles have shown that ether depresses the contractile force of the heart during surgical anesthesia to 60 to 70 per cent of the preanesthetic value.[9]

Methodological difficulties that have heretofore prohibited similar experiments with man have been overcome by recent developments in ballistocardiography. Systems that validly record cardiac force are now available.[10-17] One of these, a wide-frequency range, ultralow-frequency force ballistocardiograph,[17] has been used in the experiments reported below to show that myocardial contractile force in man is decreased during ether anesthesia.

MATERIALS AND METHODS

Each of 4 healthy 19-year-old male volunteers was given 0.4 mg. of atropine sulfate subcutaneously, placed on the ballistocardiograph 45 minutes later, and permitted to rest until his pulse and ballistocardiogram were stable. Anesthesia was induced with 225 to 600 mg. thiopental sodium given intravenously, followed by inhalation of nitrous oxide and then diethyl ether through a closed circle system equipped with a soda lime chamber. In 3 subjects anesthesia was deepened in the customary manner to Stage III, Plane 3[18] as estimated by experienced anesthesiologists. At the deepest plane, respirations were gently assisted. This level was maintained for 5 to 8 minutes. In the fourth subject, anesthesia was stopped when the subject was inadvertently allowed to emerge from Plane 2 to Stage II, and he began to cough and retch. Simultaneous ballistocardiograms, electrocardiograms, phonocardiograms, and records of the carotid pressure pulse were made at close intervals during induction and recovery.

On other occasions, control records were taken on all subjects during prolonged rest or sleep, during narcosis with 125 to 250 mg. of thiopental sodium alone, during total muscular paralysis with thiopental-succinylcholine, during inhalation of 100 per cent oxygen, and during breathing

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of a mixture of 10 per cent oxygen and 90 per cent nitrogen. One subject was anesthetized with nitrous oxide alone. Another submitted to a second session under thiopental-nitrous oxide-ether; this time he was wearing a standard Navy antigravity suit (type Z2) with bladders about the calves, thighs, and abdomen. When Stage III, Plane 3 had been reached, the bladders were inflated several times to a variety of pressures between 1 and 160 mm. Hg, and once to 320 mm. Hg.

The ballistocardiograph was that described by Reeves, Jones, and Hefner.[17,19] The table weighed 11 pounds and had a natural frequency of 0.2 cycle per second. Acceleration was sensed by the electrokinetic device of Elliott, Packard, and Kyrazis.[20] Sensitivity of the Sanborn Poly-Viso recorder was adjusted so that 300,000 dynes applied by a pendulum at heart level to the bed loaded with 100 pounds deflected the stylus 25 mm.

The maximum deflection of the ballistocardiographic I and J waves from the base line was taken as the measure of peak force represented by each. The values reported are the means from 4 or 5 waves recorded during mid-expiration.

RESULTS

1. *Thiopental-Ether Anesthesia.*—High-frequency detail disappeared from the ballistocardiograms as thiopental-ether anesthesia progressed (Fig. 1).

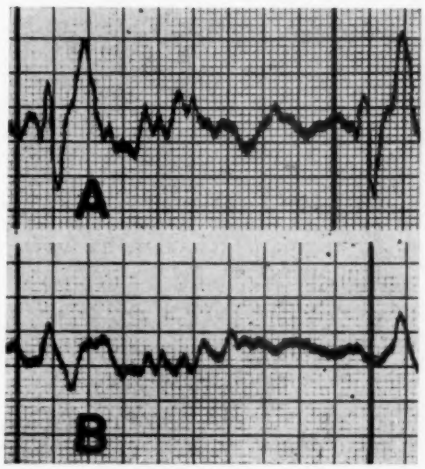

Fig. 1.—Ballistocardiogram before (*A*) and during (*B*) thiopental-ether anesthesia. Dark vertical lines are drawn at the time of the electrocardiographic Q waves. Recording speed, 50 mm./sec.

Depression of the amplitude of the I wave occurred in all subjects after the first 5 minutes (Table I and Fig. 2). At that time, the mean amplitude had decreased sharply to 71.6 per cent, ± 16.8, of the control level; it then decreased less rapidly to 40.8 per cent, ±4.4, during Stage III, Plane 3. When anesthesia was stopped, the trend downward continued for about 20 minutes to a low level of 31.2 per cent, ±3.4, of the preanesthesia level. Satisfactory records could not be obtained in all instances after that time because of artefacts derived from movements of the recovering subjects. In the two series of good ballistocardiograms, the I-wave amplitude increased.

The amplitude of the J waves was more variable than that of the I waves (Table I and Fig. 2). In two subjects it paralleled the I wave closely (Fig. 3); in one it remained between 72 and 93 per cent of the control during the entire

experiment; in the fourth, a subject who coughed when anesthesia was lightened from Stage III, Plane 2 to Stage II, the heart rate increased 175 per cent over the control, and concomitantly the J wave stopped paralleling the I wave and rose sharply from 74 to 92 per cent (Fig. 4).

The mean heart rate for the whole group varied from 97.6 per cent, ±6.2, to 114.2 per cent, ±16.2, during the anesthesia and then dropped to 88.4 per cent, ±3.0, after termination (Table I and Fig. 2). These values are greatly affected

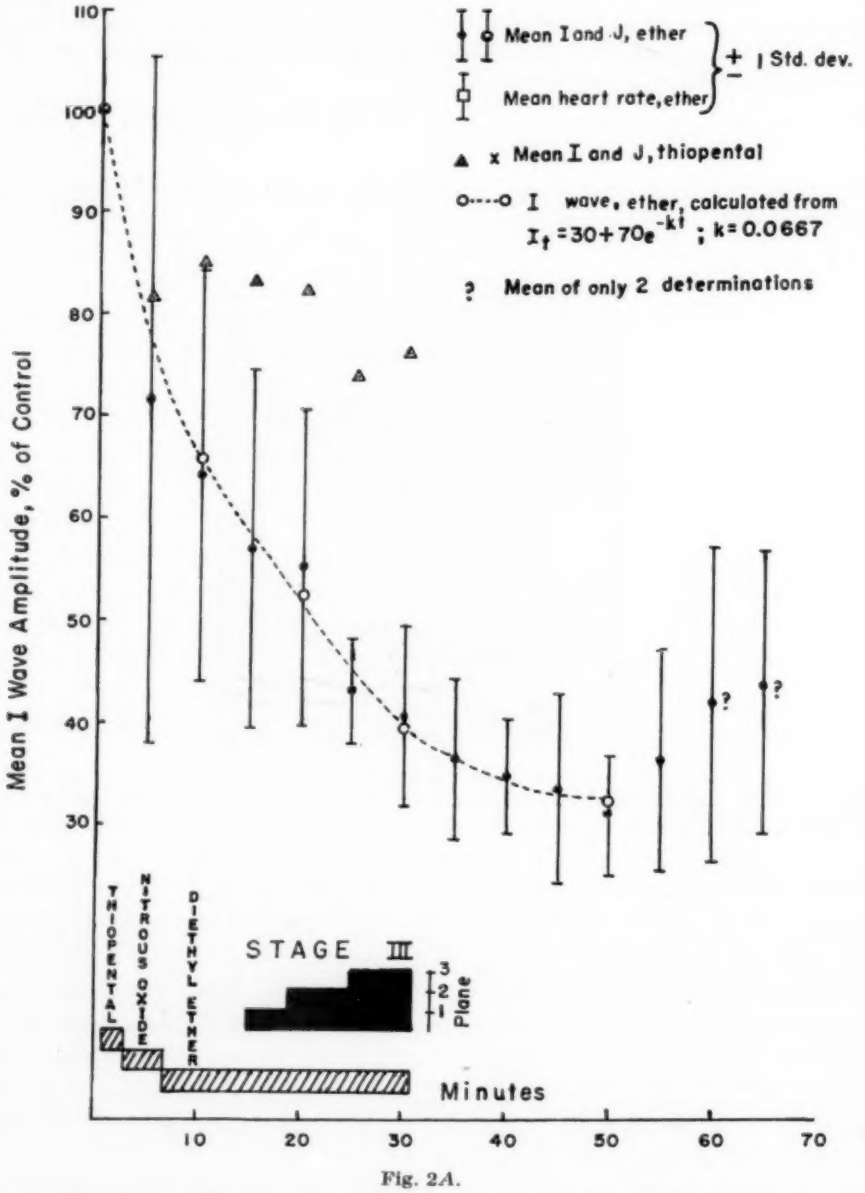

Fig. 2A.

Fig. 2.—Mean amplitudes of I and J waves (*A* and *B*, respectively) and rate of heart during thiopental-ether anesthesia in 4 subjects. The bracketed range indicates 1 standard deviation on either side of the mean; because 4 subjects were used, this range also indicates ±2 standard errors.

by the increase in rate shown by the one subject during his coughing spell. In the other three the heart rates during anesthesia were relatively constant about some point between 87 and 98 per cent, depending on the individual.

2. *Control Studies.*—Thiopental sodium alone in dosages sufficient to narcotize the subjects for 30 to 40 minutes depressed the mean I-wave amplitude to a maximum of but 74.1 per cent, ±7.9, after 25 minutes, and the J wave to 92.6 per cent, ±7.4, at the same time (Table II and Fig. 2). The probability that the difference in I-wave amplitudes during thiopental narcosis and ether anesthesia was due to chance is $0.05 > P > 0.02$ at 25 minutes and $P < 0.001$ at 30 minutes.[21]

Breathing a mixture of 10 per cent oxygen and 90 per cent nitrogen slightly increased the amplitudes of the waves; 100 per cent oxygen had little effect. The

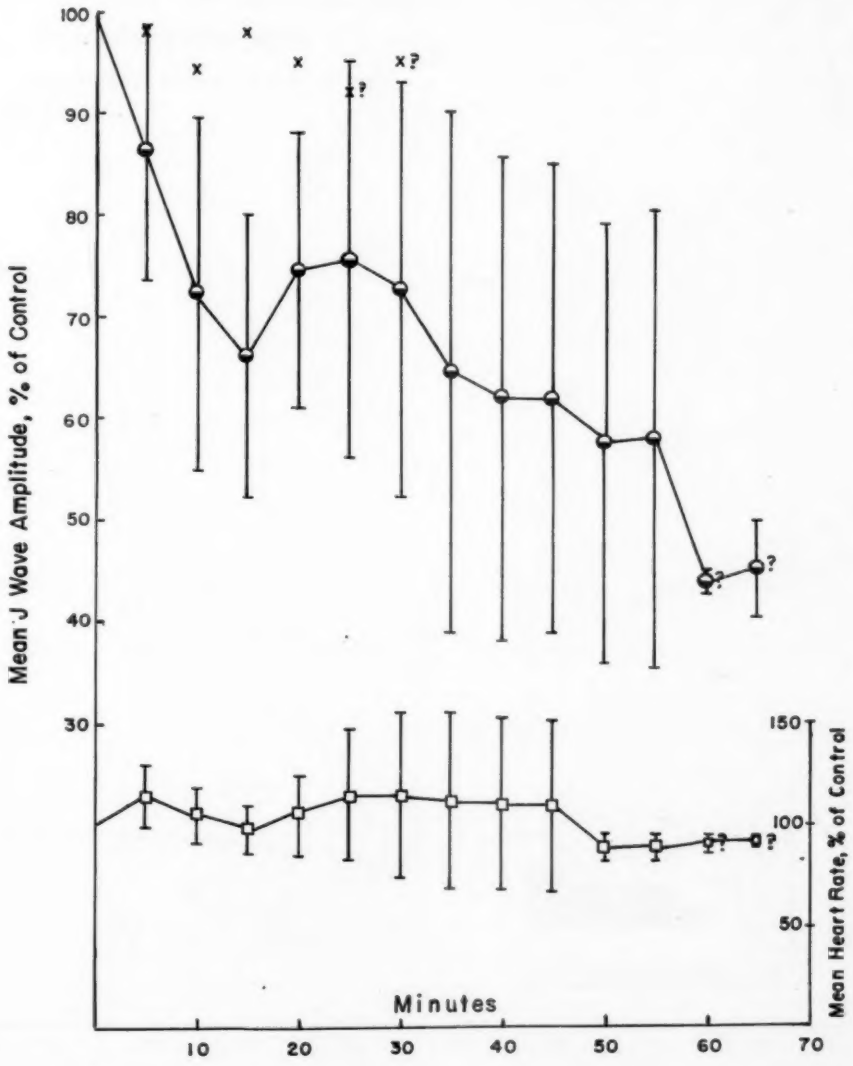

Fig. 2B. *(For legend see opposite page.)*

equivocal results produced by thiopental-succinylcholine relaxation will be reported in another paper.[22] It did not appear that the mixture served as a good control for the muscle relaxation induced by ether.

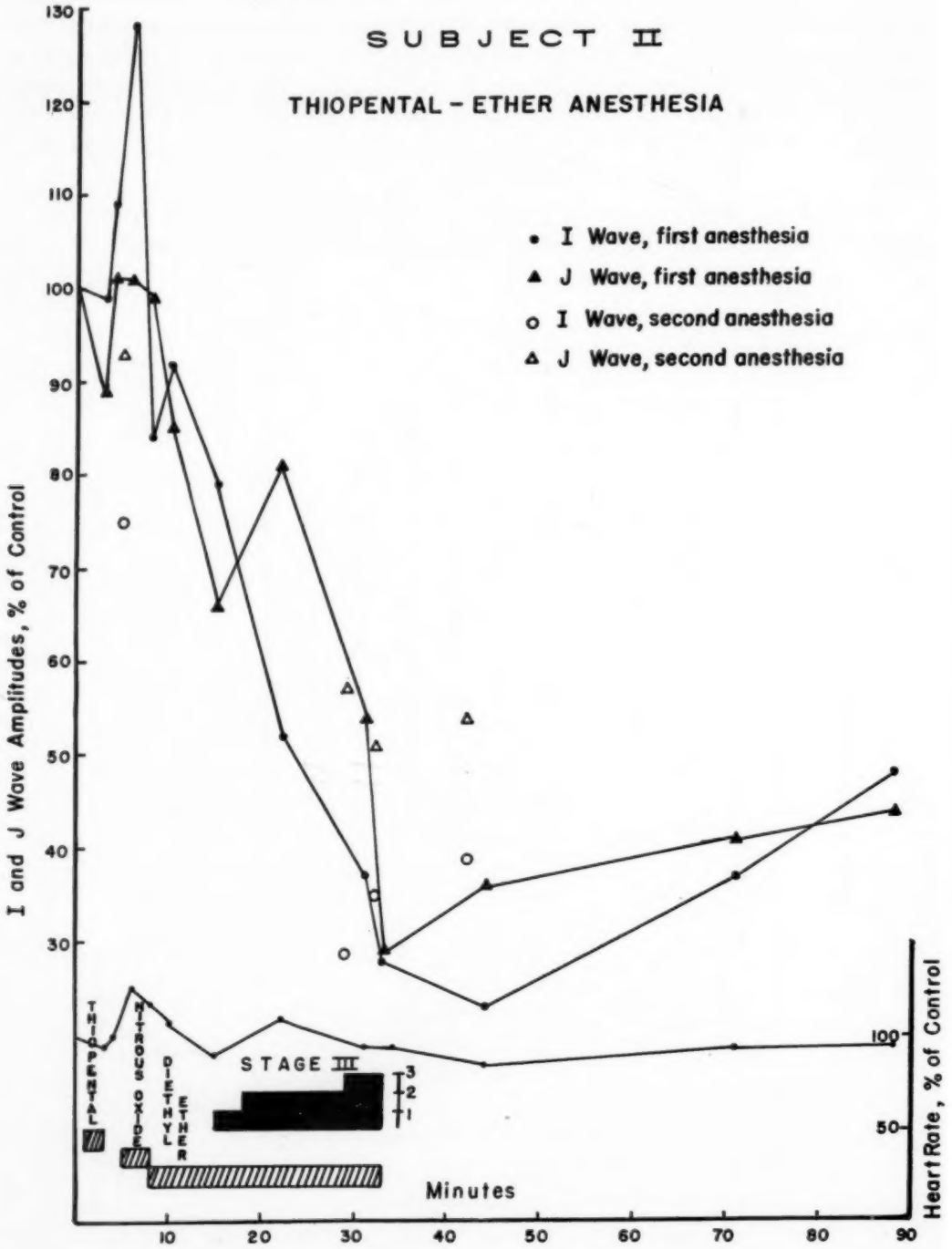

Fig. 3.—Amplitudes of I and J waves in 1 subject during two thiopental-ether anesthesias.

The only subject in whom good Stage III, Plane 1 anesthesia with 80 per cent nitrous oxide-20 per cent oxygen could be achieved showed in his ballistocardiogram an I-wave amplitude of 97 per cent and a J amplitude of 92 per cent after 8 minutes of anesthesia. These values were confirmed by a single experience with another person subjected to the same gas mixture for 30 minutes.[22]

A second thiopental-ether anesthesia in one subject produced depression of the I and J waves to about the same degree shown during the first (Fig. 3). Inflation of the antigravity suit did not effect any significant change in the ballistocardiogram. An ephemeral 5 to 10 per cent increase in height of the J wave was sometimes apparent for the first two beats following inflation.

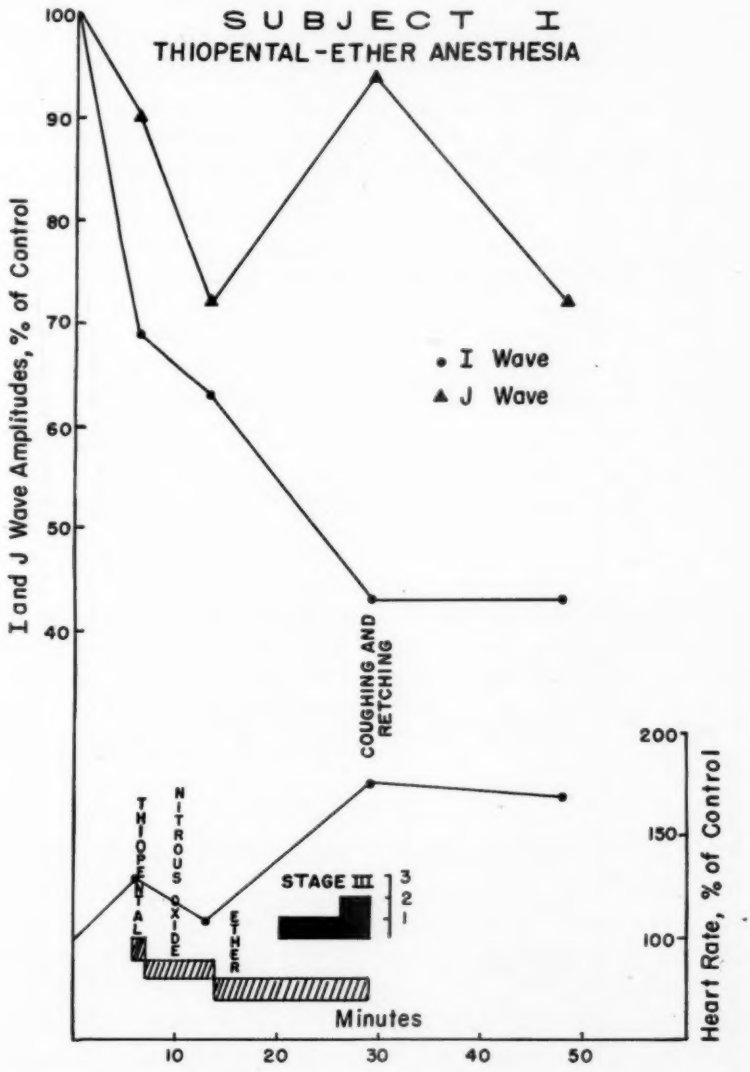

Fig. 4.—Amplitudes of I and J waves and rate of heart during thiopental-ether anesthesia of subject who began to cough and retch when inadvertently allowed to emerge from Stage III, Plane 2 to Stage II. The increase in heart rate and J waves were parallel. The I wave remained depressed in spite of the fact that stroke volume probably increased greatly.

TABLE I. AMPLITUDES OF I AND J WAVES AND HEART RATE DURING THIOPENTAL-ETHER ANESTHESIA AND INITIAL RECOVERY (PER CENT OF CONTROL VALUES)

	SUBJECT	MINUTES												
		5	10	15	20	25	30	35	40	45	50	55	60	65
I Wave	I	79.	65.5	60.5	54.2	48.	43.	43.	43.	43.				
	II	116.	92.	79.	59.5	46.9	38.6	31.	26.5	23.5	26.	28.7	31.2	33.8
	III	48.2	48.	37.5	31.	41.	51.5	43.8	36.2	28.5	39.5	52.	53.	54.
	IV	43.	51.	51.	76.	37.	30.3	28.7	33.5	40.	28.2	29.3		
	Mean	71.6	64.1	57.0	55.2	43.2	40.8	36.6	34.8	33.8	31.2	36.7	42.1	43.9
	S.D. ±	33.6	20.1	17.6	15.5	5.2	8.8	7.9	5.5	9.2	5.9	10.8	15.4	14.3
	S.E. ±	16.8	10.0	8.8	7.8	2.6	4.4	4.0	2.8	4.6	3.4	6.2	10.9	10.1
J Wave	I	88.7	78.	74.8	81.7	88.5	92.8	87.1	81.6	75.5				
	II	101.	85.	70.	77.8	72.	57.	32.	39.8	45.9	45.	44.	43.	42.1
	III	61.7	46.6	45.5	53.2	48.8	53.	55.3	43.2	40.4	39.6	39.7	43.8	48.
	IV	93.	79.6	74.2	81.	92.	87.4	82.8	83.	85.6	87.4	89.7		
	Mean	86.1	72.3	66.1	73.4	75.3	72.6	64.3	61.9	61.8	57.3	57.8	43.4	45.0
	S.D. ±	12.5	17.4	13.9	13.7	19.7	20.4	25.7	23.6	22.1	21.4	22.5	0.57	4.8
	S.E. ±	6.2	8.7	7.0	6.8	9.8	10.2	12.8	11.8	11.0	12.4	13.0	0.40	3.4
Heart Rate	I	124.2	117.	116.3	137.2	158.1	174.7	173.2	171.5	169.9				
	II	110.9	107.	90.	103.5	104.	95.7	91.2	86.6	83.3	85.2	87.	88.8	90.7
	III	126.8	108.2	102.4	97.9	100.4	98.5	96.4	98.5	100.5	98.6	95.6	93.3	91.
	IV	91.6	86.	81.6	85.	91.	87.7	84.4	80.5	79.	81.3	83.		
	Mean	113.4	104.6	97.6	105.9	113.4	114.2	111.3	109.3	108.2	88.4	88.5	91.0	90.8
	S.D. ±	15.7	13.3	12.3	22.3	30.6	40.6	43.5	42.2	42.2	6.	6.4	3.2	0.72
	S.E. ±	8.8	6.6	6.2	11.2	15.3	20.3	21.8	21.1	21.1	3.5	3.7	2.2	0.16

S.D. = standard deviation. S.E. = standard error.

TABLE II. AMPLITUDES OF I AND J WAVES AND HEART RATE DURING THIOPENTAL NARCOSIS (PER CENT OF CONTROL VALUES)

	SUBJECT	MINUTES					
		5	10	15	20	25	30
I Wave	I	96.7	93.7	90.9	99.3	85.2	77.2
	II	95.8	91.7	88.6	88.2	63.	
	III	88.8	83.	85.4	79.3		
	IV	46.	75.	73.	63.		76.
	Mean	81.8	85.8	84.5	82.4	74.1	76.6
	S. D. ±	24.1	8.6	8.0	15.2	11.1	0.8
	S. E. ±	12.0	4.3	4.0	7.6	7.9	0.3
J Wave	I	107.	102.8	99.8	101.4	103.	104.5
	II	101.	95.2	98.4	100.5	82.2	
	III	96.2	93.3	95.5	92.6		
	IV	89.9	87.	89.	88.		85.4
	Mean	98.5	94.6	95.7	95.6	92.6	95.
	S. D. ±	7.3	6.5	4.8	8.1	10.4	9.5
	S. E. ±	3.6	3.2	2.4	4.0	7.4	6.7
Heart Rate	I	115.8	117.	114.5	112.9	111.3	102.4
	II	101.4	102.6	96.	96.4	92.	
	III	112.2	115.7	105.2	99.1		
	IV	120.	89.	88.	82.5		86.
	Mean	112.3	106.1	100.9	97.7	101.6	94.2
	S. D. ±	8.0	13.1	11.5	12.5	9.6	8.2
	S. E. ±	4.0	6.6	5.8	6.2	6.8	5.8

S.D. = standard deviation. S.E. = standard error.

DISCUSSION

The data show that the ejectile force of blood headward from the apex of the heart, represented by the I wave,[19,23] was decreased early during thiopental-ether anesthesia and finally reached a level only one third of the control during Stage III, Plane 3. The amplitude of the I wave at any time during the anesthesia is expressed by the empirical formula:

$$A_t = 30 + 70e^{-kt} \qquad \text{(Fig. 2)}$$

in which A_t is the amplitude at time t (min.), e the base of natural logarithms, and k a constant with the value of 0.067. Appropriate substitution into this equation shows that the 1 per cent equilibrium level of I-wave diminution would have been reached at 82 minutes if no secondary and slower depressant mechanism were operative. The mean I amplitude at this projected equilibrium level is 30.3 per cent of the control in comparison with 31.2 per cent actually found at 50 minutes. Therefore, one would expect that continuation of the anesthesia beyond the time allowed would not have changed the results appreciably.

The J wave, representing impact force of the blood on the aortic arch and pulmonary artery bifurcation,[19,23] was less constantly affected, but, in general,

it tended to parallel the I wave at a higher level. More variable behavior of the J wave is expected, since noncardiac factors may influence its shape and amplitude.[19,23] For example, when intense excitement developed during Stage II anesthesia in one subject, the I wave continued its downhill course; the J wave reverted nearly to the preanesthetic level as the heart rate rose to 175 per cent of the control.

Administration of thiopental alone, in approximately the same dosage as used before in combination with ether, depressed the I and J waves a maximum of only 25 and 8 per cent, respectively. The conclusion is therefore drawn that, unless thiopental and ether have some as yet unknown synergistic myocardial depressant properties, the preponderant effect observed from the anesthetic mixture lay in the ether moiety. Admittedly the experiments would have been more definitive without the introduction of thiopental, but, unfortunately, a barbiturate was a necessary prelude to anesthetizing human volunteers.

Since force is the product of mass and acceleration, the recorded decrease indicates an actual reduction in myocardial contractile force only if the mass to which acceleration was imparted remained constant or increased. This mass, the stroke volume, was not determined. However, it is known that heart rate and cardiac index correlate in etherized man with a coefficient of 0.7,[24] so that it is unlikely that the slight changes in rate shown by three of the four subjects were associated with significant decreases in cardiac output, or, by inference, in stroke volume. Furthermore, in the subject who had the attack of coughing and in whom stroke volume certainly increased appreciably, force remained low. Finally, had a decrease in ejected mass been responsible for the diminished ballistic force, stroke volume would have had to be reduced to about one third of the preanesthetic value. No patient in Fletcher's[24] series of eleven and only one in Johnson's[25] fourteen showed such a great fall in volume; after 30 minutes of anesthesia not one of the other 24 patients was even below two thirds of the control, and most were considerably higher.

Perhaps the strongest objection to this line of reasoning comes from analogous work with dogs. Scarborough[26] found that pentobarbital-morphine anesthesia caused a loss of high-frequency detail and a depression of amplitude similar to that found in the records of human subjects. His crucial observation was that the abnormal ballistocardiogram was almost certainly a result of low stroke volume, because abdominal compression, which compressed the splanchnic bed and augmented venous return and stroke volume, restored the records to normality. That a similar phenomenon is probably not operative in man, however, was shown by the experiment with the human subject in the antigravity suit. Not only did this study show that compression of the calves, thighs, and abdomen did not change the ballistocardiogram, but it confirmed the original observations and added to the presumption that ether affects the contractility of the heart in a manner predictable from the empirical equation. Moreover, Hill's[27] experiments indicate that there are great qualitative differences in the effect of ether as contrasted with other agents on splanchnic pooling, for ether paralyzes compensatory vasomotor mechanisms only slowly and when used in "enormous" amounts.

These considerations make it unlikely that a change in mass accounted for any significant part of the change in force. They strongly suggest that the acceleration given the blood, and hence the contractile force of the heart, is decreased during ether anesthesia. This finding is compatible with the results from experiments cited above,[1-9] with the contention of Fletcher, Pender and Wood[24] that the increased venous pressure found during ether anesthesia was a reflection of myocardial incompetence, and with the conclusion of Sutton, Little and McClung[28] that delayed electrical and mechanical responses of the myocardium during anesthesia implied a cardiac depressant effect of ether.

SUMMARY

Force ballistocardiograms from an ultralow-frequency system were recorded on 4 healthy young volunteers during thiopental-ether anesthesia, thiopental narcosis, and other related states. During Stage III, Plane 3 thiopental-ether anesthesia, the contractile force of the heart decreased to approximately one third of the control value. Collateral evidence suggests that ether was the cause of the myocardial depression.

Indispensible help was generously given by Drs. Robert E. Walsh and Richard C. Woellner in administering ether anesthesia, and by Drs. William R. Scarborough, Henry K. Beecher, and P. Franklin Mullinax, Jr. in interpreting the data and criticizing the manuscript.

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An Analysis of Changes in the Spatial Vectorcardiogram With Aging

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The spatial vectorcardiographic method of displaying electrical activity associated with the cardiac cycle often renders recognizable minor alterations not readily detectable in the conventionally recorded electrocardiogram. The normal spatial vectorcardiogram of man at various ages, however, has never been defined. The present study, therefore, was undertaken in an attempt to determine the influence of the normal aging process on the spatial vectorcardiogram (sVCG).

MATERIALS AND METHODS

Two hundred and twenty-three clinically normal subjects (159 men and 64 women) between the ages of 20 and 68 years were used in this study. The group included medical students, postgraduate physicians, and persons examined in the Cancer Detection Clinic of the Tulane University School of Medicine.

Spatial vectorcardiograms were recorded with the use of the cathode-ray oscilloscope and the equilateral tetrahedral reference system. Details of this method of recording have been described elsewhere.[1] The records included projections of the sVCG on the frontal, right, left, and superior planes of the equilateral tetrahedron, and stereoscopic views of these projections, as well as left sagittal projections of each of the aforementioned planes. Wire models of each sVCG were constructed for proper orientation of the loop in space. All measurements were obtained from enlargements of the recordings made on 35 mm. film.

RESULTS

Measurements of the QRS and TsÊ loops for the subjects over 30 years of age are summarized in Table I. Similar data for subjects in the third decade of life have already been reported.[2] The magnitude and direction of the frontal plane projection of the maximal mean instantaneous vectors of the QRSsÊ loops were strikingly similar throughout all age groups (Table I).[2] In most instances

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TABLE I. MEASUREMENTS OF QRS AND TsÊ LOOPS IN 152 NORMAL SUBJECTS

AGE (YR.)	NUMBER OF CASES	QRSsÊ LOOP				TsÊ LOOP			
		FRONTAL		SAGITTAL		FRONTAL		SAGITTAL	
		ANGLE (DEGREES)	LENGTH (MV.)	ANGLE (DEGREES)	LENGTH (MV.)	ANGLE (DEGREES)	LENGTH (MV.)	ANGLE (DEGREES)	LENGTH (MV.)
30–39	58	min. − 16	0.20	−100	0.25	− 13	0.11	−158	0.07
		max. + 90	1.35	+153	1.42	+146	0.43	+171	0.38
		av. + 53	0.77	+ 96	0.65	+ 43	0.22	+131	0.19
40–49	53	min. − 22	0.34	−171	0.20	− 5	0.10	−178	0.09
		max. +116	1.62	+142	1.18	+ 80	0.34	+173	0.84
		av. + 41	0.81	+ 88	0.58	+ 38	0.23	+134	0.22
50–59	34	min. −103	0.33	− 53	0.23	+ 14	0.12	+ 96	0.09
		max. + 90	1.33	+165	1.37	+150	1.28	+169	1.32
		av. + 33	0.69	+109	0.53	+ 50	0.26	+142	0.22
60–69	7	min. − 44	0.52	− 46	0.25	+ 48	0.20	+122	0.22
		max. + 68	0.80	+170	0.70	+ 88	0.28	+136	0.28
		av. + 35	0.66	+132	0.49	+ 41	0.17	+ 92	0.18

the direction of inscription of the QRSsÊ loops was clockwise in the frontal plane projection (77 per cent) and counterclockwise in the left sagittal plane projection (88 per cent), just as was noted for the subjects in the third decade of life. The maximal posterior deflection of the QRSsÊ loops in the left sagittal plane projection was found to be approximately the same in all groups (mean 0.16 mv.) except the oldest, in which it was of smaller magnitude (mean 0.09 mv.).

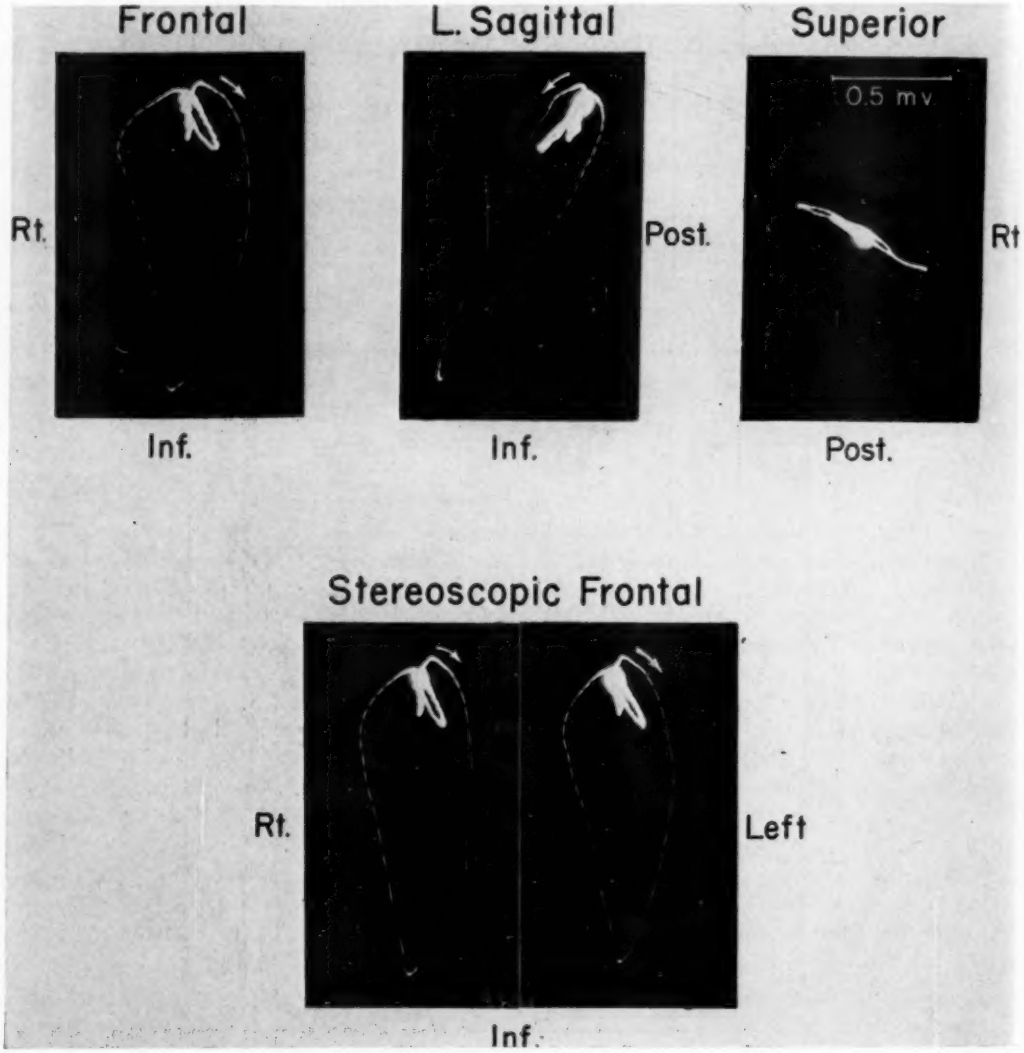

Fig. 1.—This QRSsÊ loop of a 52-year-old male physician is typical of normal tracings without evidence of distortion. The arrow indicates the direction of inscription of the tracing. See corresponding electrocardiogram in Fig. 4,*A*.

"Distortion," or pronounced irregularity in contour, of the QRSsÊ loop, which had been noted for the past several years, was further emphasized in the wire models of these loops. This was manifested by a straight initial or terminal portion of the QRSsÊ loop or by single or multiple abrupt, nonartifactitious

changes in spatial time course in any portion of the loop. The typical smooth QRSsÊ loops previously described for normal medical students[2] were used as standards for comparison. According to the degree of distortion, loops were divided into 3 major groups: (1) undistorted (Fig. 1), (2) unequivocally distorted (Fig. 2), and (3) questionably distorted (Fig. 3). Although no attempt was made to grade the degree of distortion, it was observed to be more pronounced in some loops than in others.

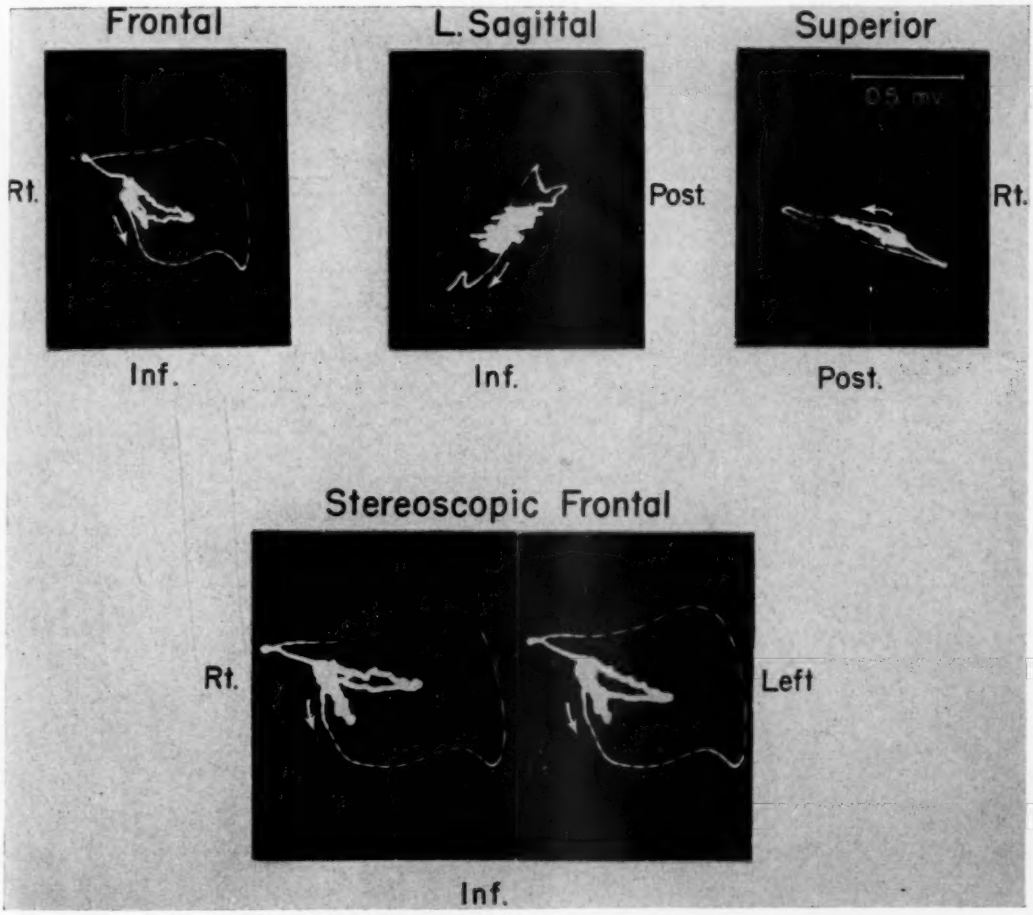

Fig. 2.—This QRSsÊ loop of a 51-year-old man shows definite evidence of distortion. Multiple major changes in the direction of the time course of depolarization and straightening of the initial portion of the loop are evident. The distortion in the sagittal to the frontal plane cannot be attributed to the artifact at the isoelectric point, since the artifact cannot be seen in the other projections, whereas the distortion persists. See corresponding electrocardiogram in Fig. 4,*B*.

The incidence of distortion increased directly with each succeeding decade of life of the subjects: 22.5 per cent in the third, 29.3 per cent in the fourth, 52.8 per cent in the fifth, and 67.7 per cent in the sixth (Table II). The QRSsÊ loops were definitely distorted in the spatial vectorcardiograms of all 7 subjects over 60 years of age. One patient beyond the age groups included in this series (72 years old), however, did have a questionably distorted QRSsÊ loop.

TABLE II. INCIDENCE OF DISTORTION OF THE QRSsÊ LOOP IN 223 NORMAL SUBJECTS

CONFIGURATION OF QRSsÊ LOOP	AGE (YEARS)											
	20–29		30–39		40–49		50–59		60–69			
	CASES		CASES		CASES		CASES		CASES			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT		
Undistorted	42	59.2	33	56.9	20	37.8	6	17.6	0	0		
Distorted	16	22.5	17	29.3	28	52.8	23	67.7	7	100		
Questionably distorted	13	18.3	8	13.8	5	9.4	5	14.7	0	0		
Total	71		58		53		34		7			

DISCUSSION

As the age of the patients increased, the configuration and spatial orientation of their QRSsÊ loops became altered, despite the absence of any detectable clinical evidence of cardiac disease or readily discernible changes in the conventionally recorded electrocardiogram (Fig. 4). Distortions involved all portions of the QRSsÊ loop and were particularly common in the loops of subjects beyond the fourth decade of life.

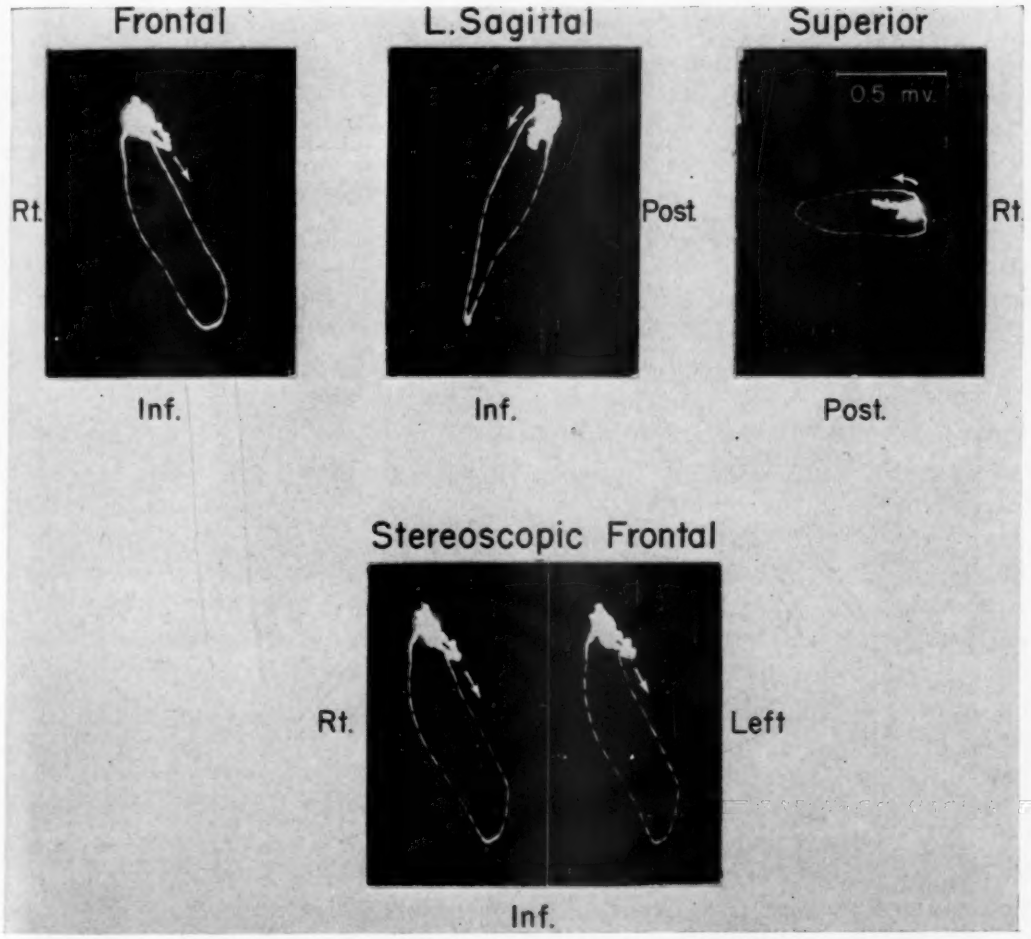

Fig. 3.—This QRSsÊ loop of a 36-year-old woman shows questionable evidence of distortion. The central and terminal portions of the loop are distinctly straight, whereas the remainder of the trace appears smooth. See corresponding electrocardiogram in Fig. 4,*C*.

The mechanisms responsible for the development of these deformities are unknown. Cardiac, as well as extracardiac, factors may have contributed, but myocardial changes, resulting in alterations in the time course of depolarization, were most likely responsible for these. Slight injury to the myocardium, associated with "wear and tear," coronary arteriosclerosis with minute areas of myocardial destruction and replacement with fibrosis, as well as functional

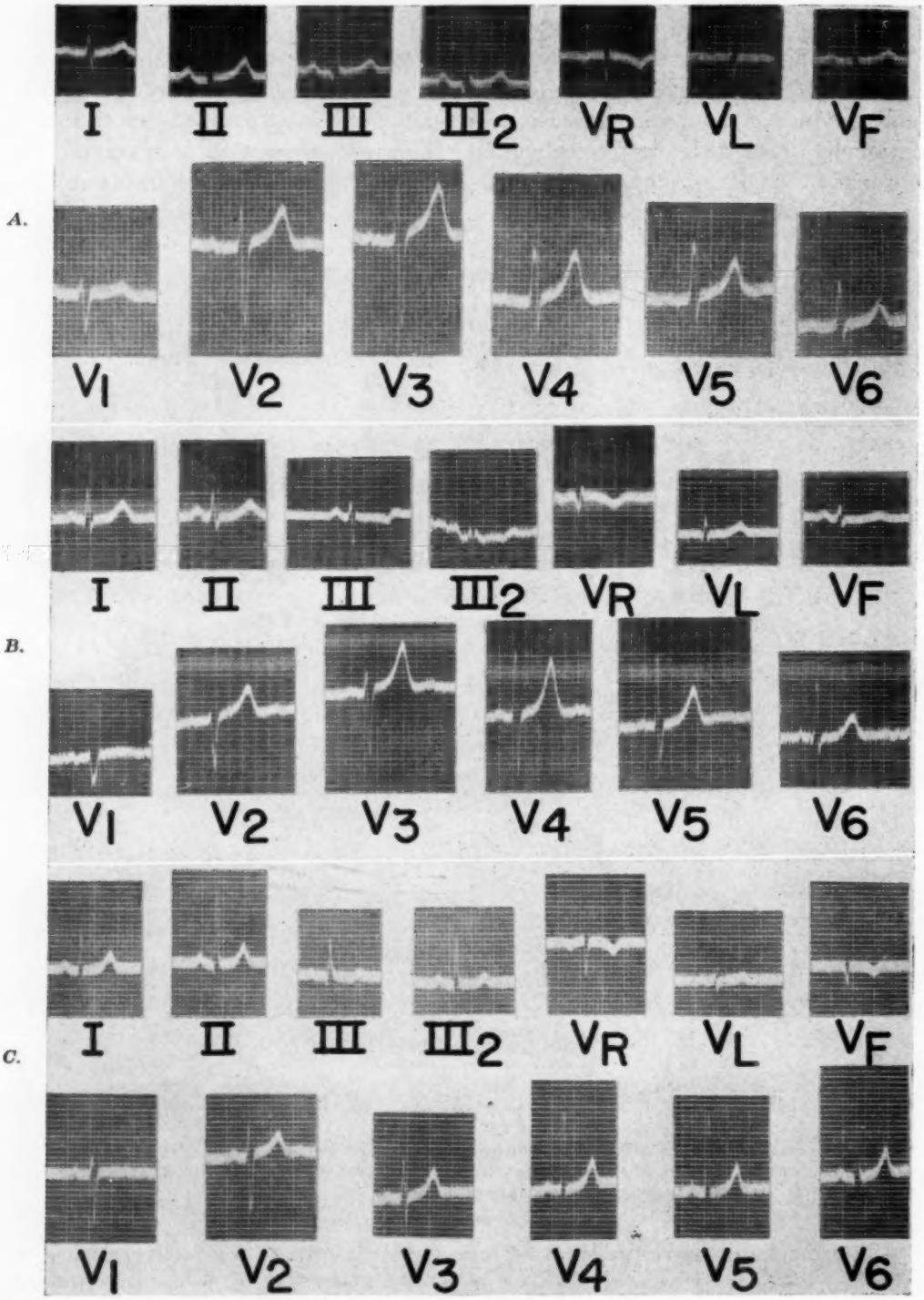

Fig. 4.—Normal electrocardiograms recorded simultaneously with spatial vectorcardiograms shown in preceding figures. *A*, 52-year-old male with undistorted sVCG—corresponds to Fig. 1. *B*, 51-year-old male with unequivocally distorted sVCG—corresponds to Fig. 2. *C*, 36-year-old woman with questionably distorted sVCG—corresponds to Fig. 3.

and molecular change without necessarily demonstrable histologic changes, all occur with aging and, in turn, produce alterations in the cardiac electrical behavior.

Whereas vectorcardiographic alterations with natural aging may not be considered abnormal, they may possibly assist in evaluation of the cardiac status. Distortions in the sVCG may reflect clinically significant cardiac changes associated with aging and may serve as an index of this process, like gray hair, wrinkled skin, and other such well-known manifestations. Furthermore, certain distortions in the sVCG may conceivably represent premonitory manifestations of serious disease, although such relations have not yet been investigated.

The sVCG has the advantage over the conventionally recorded electrocardiogram of providing greater detail of the manifested electrical activity of the heart. An electrocardiogram recorded with a galvanometer that has a wide frequency range and with recording paper driven at a higher speed might reveal similar alterations, as suggested by Langner.[3] Some of the more pronounced distortions of the QRSsÊ loop had detectable electrocardiographic counterparts, such as slurs and notches of the QRS complex. In some instances, however, the electrocardiographic changes would have remained unrecognized had the distortions in the sVCG not suggested them. Subtle changes that occur in the electrocardiogram with advancing age require further investigation.

Whereas alterations in the time course of depolarization produced by the natural aging process seem to be primarily responsible for the distortions noted in the QRSsÊ loops in this study, extracardiac changes that occur with age (emphysema, and anatomic displacement and rotation of the heart) may also have contributed. In fact, the tendency for the QRS and TsÊ loops to be oriented more horizontally in the older subjects is probably the result of cardiac displacement in the thorax.[4] Emphysema would alter the electric characteristics of the tissue surrounding the heart. Displacement of the heart would further modify the spatial relations of the surrounding structure, the electric field around the heart, and, in turn, the time course of the recorded manifested electric potentials would be altered. The simultaneous time courses of the magnitudes of the respective cardiac and the extracardiac factors responsible for the distortions in the sVCG must be thoroughly known in order to understand better the significance of such distortions associated with the aging process.

The undistorted and distorted vectorcardiograms were readily identified, but a number of tracings could not be classified with certainty in either category. These were considered equivocal and may have represented records that were undergoing changes too slight to fulfill definitely the criteria of distortion. Serial records would probably clarify the ambiguity, for any early, slight distortions produced by aging should become progressively more pronounced as the subject grows older.

SUMMARY

Spatial vectorcardiograms of 223 normal subjects between the ages of 20 and 68 years have been analyzed in an attempt to determine changes attributable to the normal aging process. Distortion of the QRSsÊ loops of the sVCG, or

pronounced irregularity in the time course of the wave of depolarization, was observed with increasing frequency as the age of the patient advanced. Although no arbitrary decision could be made in all cases, most spatial vectorcardiograms could be separated into those with and without distorted QRSsÊ loops. The mechanism of the changes remains unknown but seems attributable in large part to alterations with age in the time course of depolarization. More extensive investigation of a larger series of subjects of various ages, involving serial tracings, is necessary to elucidate the clinical significance of the distortions.

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Myxoma of the Left Atrium: Report of Three Cases

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Approximately 150 cases of myxomas have been reported up to April, 1955.[1] It is probable that they are not that rare. Many cases might have been missed because they could not be diagnosed during life and because no post-mortem examination was performed. We found recently, within 1 month, 2 cases of myxoma of the left atrium on post-mortem examination. Previously, only 1 myxoma had been found in 3,000 consecutive autopsies. (Approximately 60 per cent of our male patients are 50 years of age or older and more than 99 per cent are males.)

Since surgical removal of myxomas is now possible (and several myxomas have been successfully removed under hypothermia), their recognition is of more than academic importance.[2,3] The purpose of this paper is to make a further contribution to this subject by reporting 3 cases.

CASE REPORTS

CASE 1 (N. A., No. 122 099).—This 63-year-old white man was admitted to the hospital because of marked dyspnea on exertion, orthopnea, and ankle edema which started 1 month prior to admission. The patient had been suffering from bronchial asthma for the past 20 years. Three years prior to admission he had an attack of precordial pain, which radiated across the chest and was relieved by rest.

Physical Examination.—The blood pressure was 130/70 mm. Hg. The cardiac rhythm was regular. No murmurs were heard. The heart was enlarged 1.5 cm. to the left of the midclavicular line. The pulmonic second sound was accentuated. There was left pleural effusion. The liver extended 2 fingerbreadths below the costal margin. There was 4-plus leg edema. X-ray of the chest showed left pleural effusion and calcification of the aortic knob. The electrocardiogram showed flat T waves. Urinalysis, hematogram, and blood chemistry were noncontributory. While in the hospital the patient was digitalized and given diuretics to which he responded. On Oct. 4, 1956, the patient had a sudden attack of syncope and became pulseless, but recovered. This was interpreted clinically as shock of coronary occlusion. However, when the patient was being examined, one observer considered the possibility of a myxoma in the differential diagnosis, because he had recovered a few minutes after the attack. On Oct. 7, 1956, the patient had a similar attack and expired.

Post-Mortem Examination.—Pertinent findings were limited to the heart and lungs. The heart weighed 650 grams. There was dilatation of the right ventricle with mild hypertrophy, and marked hypertrophy of the left ventricle. Upon opening the heart a multilobulated tumor,

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measuring 8 cm. in diameter, was found. It filled the left atrium, obstructing the mitral inlet. It was attached to the closed foramen ovale by a narrow fibrous stalk 3 mm. in diameter. The tumor mass was of a gelatinous consistency. Posterior to this large tumor there was a smaller group of myxomatous lobules forming a mass only 4 cm. in diameter but showing a broader base of attachment than the larger tumor. The auricular appendages were free from mural thrombi (Fig. 1). The valve leaflets were thin and pliable. The aorta showed moderate generalized atherosclerosis. The coronary arteries showed extensive atherosclerosis with marked narrowing of the lumina in all major branches, but no complete occlusion.

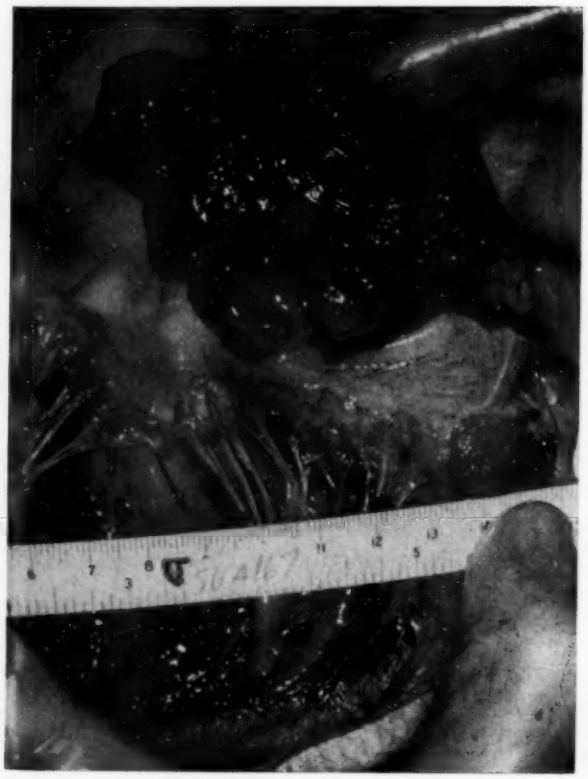

Fig. 1.—Case 1. See text.

Histologically, the tumor varied from field to field. There were definite myxomatous areas with pink glassy stroma and thin elongated cells showing a stellate tendency (Fig. 2). Other fields showed indisputable characteristics of an organizing thrombus with young, active fibrocytes, red blood cells, and hemosiderin-laden phagocytes.

CASE 2 (H. J. E., No. 115 325).—This 80-year-old man was disorientated on admission to the hospital and died 3 days later. Generalized arteriosclerosis had been diagnosed 3 years prior to admission.

Physical Examination.—The blood pressure was 110/70 mm. Hg. The respiration was rapid, and neck veins were distended. There were râles in both lung bases posteriorly. The heart rate was rapid. No murmurs were heard. X-ray of the chest showed acute bronchopneumonia involving both lung bases and a normal-sized heart. The electrocardiogram was normal. Blood count and urinalysis were noncontributory. Nonprotein nitrogen was 65 mg. per cent.

Post-Mortem Examination.—Pertinent findings were limited to the heart and lungs. The lungs showed massive consolidation of both lower lobes and the right middle lobe, with the pres-

ence of a plastic pleural exudate. There also was bronchiectasis of the left lower lobe. The heart weighed 300 grams; the right ventricular wall was slightly thickened; the valve leaflets were delicate. In the left atrium, near the closed foramen, there was a flat, slightly elevated, mushroom-like, tannish-red mass measuring 1 cm. in greatest diameter. The coronary arteries showed relatively mild, diffuse, atheromatous changes consistent with the age of the patient. The lumen was patent throughout. The abdominal aorta showed moderately severe atheromatous changes.

Microscopic Examination.—The tumor showed a large amount of phagocytized blood pigment. The stroma was quite delicate and contained a few elongated and stellate-shaped cells. There also were lymphocytes and plasma cells present (Fig. 3). Death resulted from massive bilateral bronchopneumonia, and the myxoma of the left atrium constituted an incidental finding.

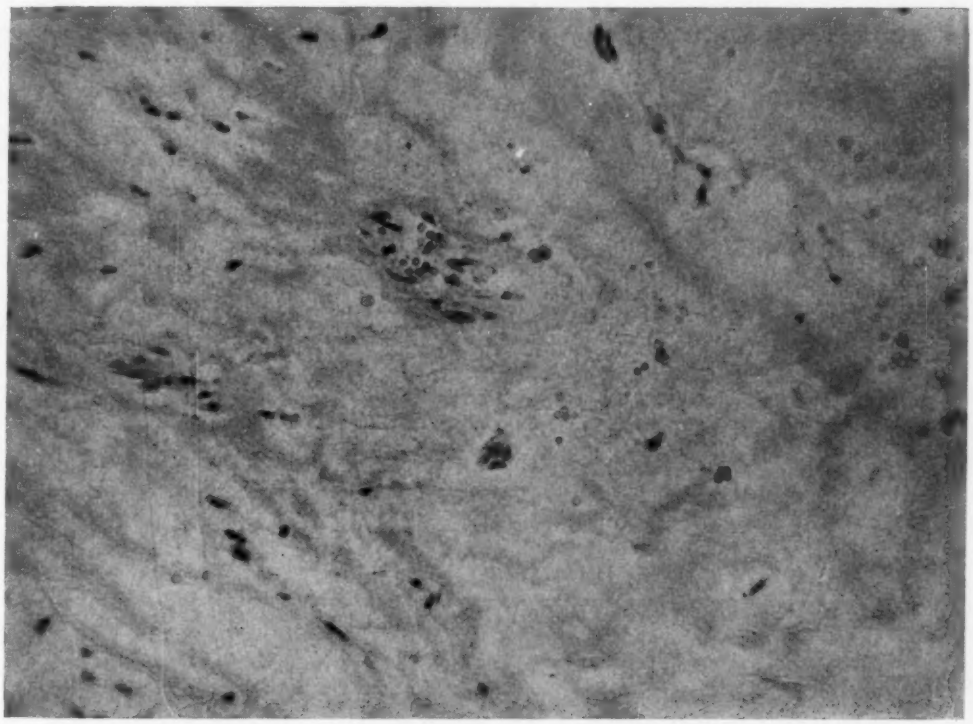

Fig. 2.—Case 1. See text.

CASE 3 (S. F. A., No. 123 181).—This 79-year-old white man had a history of recurrent cardiac decompensation, which started in 1955, one year prior to his last admission. He was treated at that time with digitalis, to which he made a good response. The patient remained on a maintenance dose of digitalis and felt relatively well until a few days before his final admission in November, 1956, necessitated by shortness of breath and edema of the legs.

Physical Examination.—Examination showed an increase in the anteroposterior diameter. There were frequent ventricular premature contractions present. There was a Grade 2 systolic apical murmur present. The aortic second sound and the pulmonic second sound were equal. The liver was 2 fingerbreadths below the costal margin. There was 3-plus pitting edema. The blood pressure was 110/90 mm. Hg. X-ray of chest showed cardiac enlargement, mostly of the left ventricle, although some right ventricular hypertrophy was also present. The electrocardiogram showed right bundle branch block, frequent premature contractions, and digitalis effect.

Post-Mortem Examination.—There were numerous pulmonary infarcts with superimposed pneumonitis. The heart weighed 810 grams. The left atrium was completely filled by a large,

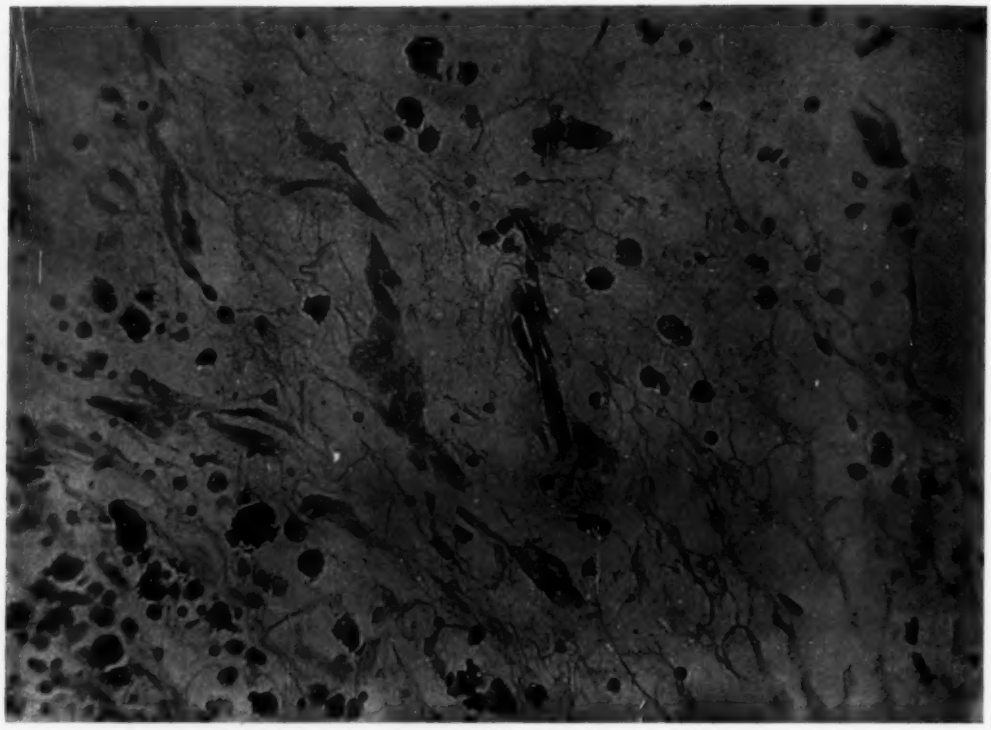

Fig. 3.—Case 2. See text.

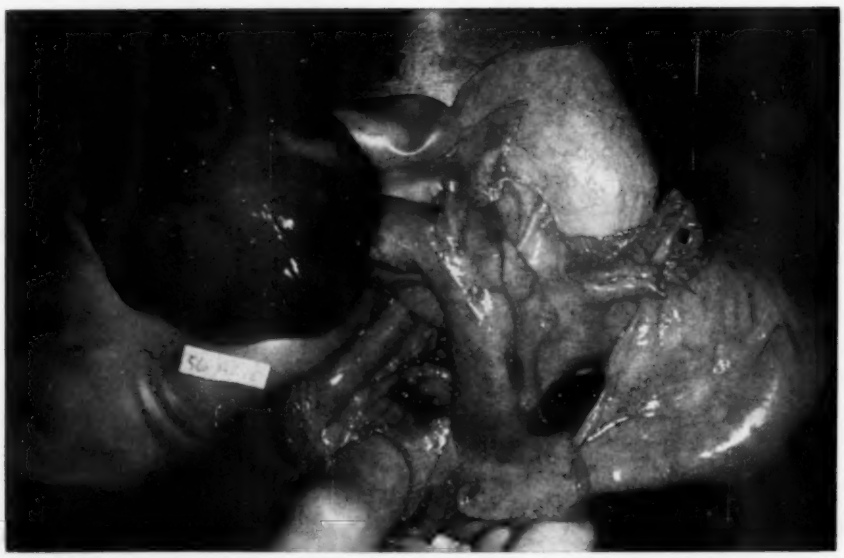

Fig. 4.—Case 3. See text.

smooth, round, fatty tumor measuring 7 cm. in diameter, which almost completely obstructed the mitral inlet. The myxoma arose just above the foramen ovale and was attached to the atrial wall by a narrow fibrous stalk 1 cm. in diameter (Fig. 4).

On sectioning, the mass showed a gelatinous, pale yellow color. The right ventricle and right atrium were markedly dilated. The right ventricle measured 0.5 cm. in thickness, the left ventricle 1.3 cm. in thickness. In the right auricular appendage there was a mural thrombus which was probably the source of the bilateral pulmonary emboli. The heart valves were thin and pliable. The coronary arteries showed extensive atherosclerosis of the left anterior descending branch. The aorta showed mild arteriosclerosis.

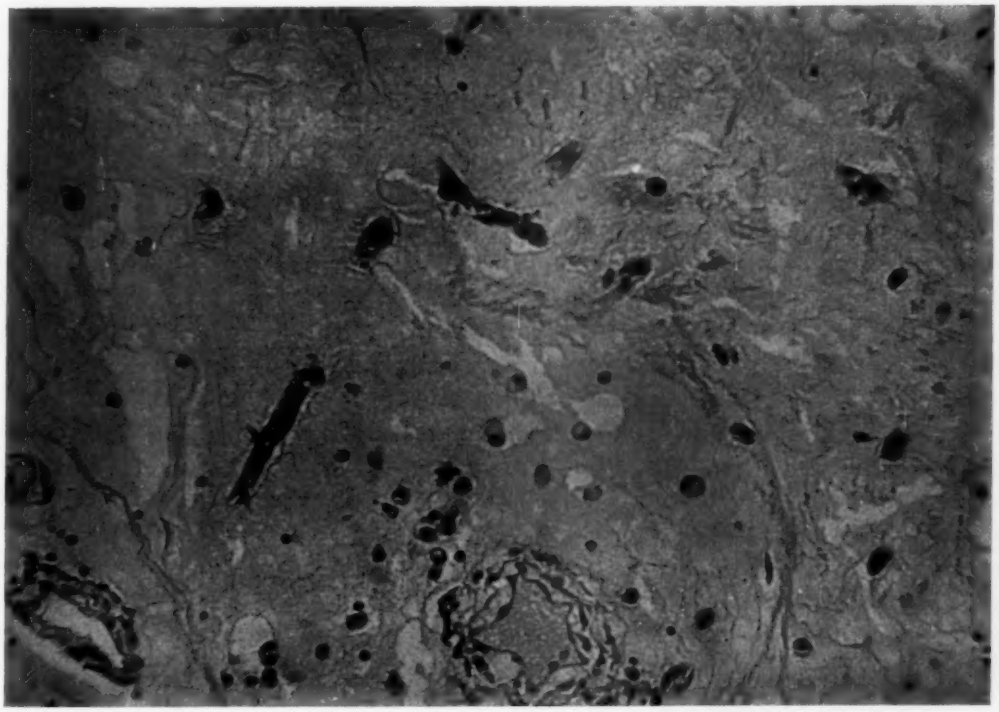

Fig. 5.—Case 3. See text.

Microscopic Examination.—Two sections through the myxoma showed a typical architecture with a large amount of a slightly blue matrix, containing small numbers of nuclei, which varied considerably in size and shape. The majority of the nuclei were long and slender. Vascular channels were quite numerous (Fig. 5). The final diagnoses were large pedunculated myxoma of the left atrium, marked dilatation of the right atrium and right ventricle, organizing thrombus, right auricular appendage, and coronary atherosclerosis.

DISCUSSION

The myxomas comprise one half of all primary cardiac tumors.[1] They are more frequent in women.[4]

The clinical recognition of a myxoma is rather difficult, and it is, therefore, not surprising that most are not diagnosed during the patient's life but are incidental post-mortem findings. The absence of history of rheumatic fever in a myxoma is of no help in the differential diagnosis because approximately 50 per

cent of proved cases of rheumatic mitral stenosis do not give a history of rheumatic fever, in spite of the most accurate and detailed questioning. On the other hand, a history of rheumatic fever has been encountered in some cases of myxoma.[5]

Rapid and progressive cardiac failure is suggestive of a myxoma, because mitral stenosis usually responds initially to digitalis treatment.[5,6] However, this is not always the case, and frequently, as in our Case 3, the patient has been digitalized previously with good response. Of course, it is possible that our Case 3 did not have a myxoma at the time he responded to digitalization, that is, one year prior to his death. It is not known how long a patient can live with a myxoma, nor for how long a myxoma is asymptomatic. Even post-mortem examination cannot determine the duration of the myxoma. It has been stated, however, that the clinical course of a patient with a myxoma is rather short.

Dyspnea disproportionate to the degree of the enlargement of the left atrium is more suggestive of a myxoma. However, this is difficult to evaluate. As a matter of fact, 2 of our patients were not dyspneic. The dyspnea depends on the size of the tumor and how much it obstructs the blood flow. In other words, how much it mimics the picture of mitral stenosis.

Many cases of myxoma simulating mitral stenosis have been reported. The character of the murmur changes with the change of position of the patient.[1,2,7,8] Even an opening snap in a case of a myxoma has been reported.[9] This is probably one of the most important clinical features in the differential diagnosis, provided one thinks of this possibility and has the opportunity to follow the patient during these attacks. If the tumor is not fixed there will, of course, be a change in the character of the murmur with change of position, and if the tumor on change of position obstructs the mitral inlet there will be a clinical and auscultatory picture of mitral stenosis.[5,6,7] Case 1 became pulseless on two occasions while reclining; his pulse was felt again with change of position. The possibility of a myxoma of the left atrium was considered in the differential diagnosis.

When the patient changes his position, the tumor may occasionally be shifted in such a way that it obstructs completely the orifices of the mitral valves, with resulting sudden attacks of fainting, cold and clammy skin, absence of peripheral pulses, breathlessness, and cyanosis. The signs may disappear with the change of position, such change relieving the obstruction of the mitral inlet. Sudden death may occur if the obstruction caused by change of position lasts long enough.[1,10] However, several cases of proved myxomas have been reported in which there was no change of the murmurs with a change of position.[7] This is easy to understand, because in cases in which the tumor is fixed there will be no change of murmurs with change of position of the patient. Then too, the tumor may be fixed in such a way that it will never reach the mitral inlet no matter how the patient changes his position; and in such a case the tumor is, of course, not diagnosable. Electrocardiograms are not helpful in the differential diagnosis of auricular myxomas.[5]

Cardiac catheterization has been performed on several patients,[11] with findings of evidence of obstruction at the mitral valve, consisting in elevation

of the left atrial and pulmonary capillary pressures. All that cardiac catheterization can do is to confirm the hemodynamic pattern of mitral stenosis (if a pedunculated myxoma partially occludes the mitral inlet).

Angiocardiography is the only method for making a definite diagnosis of a myxoma of the atrium, because it shows a characteristic filling defect in an enlarged left atrium.[6,11] Of course, in an elderly patient in terminal condition there is no way of proving this presumptive diagnosis.

There is still controversy as to whether a myxoma represents a true neoplasm or whether it is a thrombus undergoing myxomatous degeneration. Several authors, especially those of the older literature, were of the opinion that myxomas were organized thrombi which had undergone myxomatous degeneration.[12,13] This opinion was based on the fact that patients had congestive failure with formation of thrombi elsewhere in the body, and also because in many tumors there were numerous plump fibroblasts. In the recent literature a case of myxoma considered to be an organized thrombus has been reported.[7]

Many authors[10,14-17] have been of the opinion that myxomas are true tumors because: (1) The great majority of the myxomas occur in the left atrium. (2) There is frequently no evidence of thrombus formation in the auricular appendage. (3) If myxomas were organized thrombi, one would expect them to occur in the ventricles where thrombi are common. (4) There is no evidence of stratification in myxomas, which is so common in thrombi. (5) Microscopically myxomas contain stellate cells, which are sometimes large and multinucleated. (6) Lymphocytes and plasma cells are often seen in the tumor. Other authors[18] have taken an intermediate view and thought that myxomas were pseudo-myxomas or pedunculated thrombi. Some have even thought that they were endotheliomas.[19]

The tumors of the 3 cases reported here fit both the gross and microscopic criteria for myxomas. However, we are unable to prove whether they are true neoplasms or organized thrombi.

SUMMARY

Three cases of myxomas of the left atrium are reported together with the post-mortem findings.

Myxomas are probably more frequent than would appear from the literature.

The diagnostic and differential diagnostic features of myxomas are discussed. It is stressed that the only way of making a diagnosis of myxomas is to keep in mind the possibility of their existence. Angiocardiography is the only objective means of making a diagnosis.

The histological structure of our cases does not allow any conclusions as to whether these 3 myxomas are true neoplasms or organizing thrombi undergoing myxomatous degeneration.

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Central and Femoral Pressure Pulses in Aortic Valve Diseases: A Quantitative and Qualitative Analysis

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A previous report[1] quantitatively described the central and femoral pressure pulses in dogs with normal and incompetent aortic valves. In the present study the technique of central aortic catheterization was used to record pressure pulses in patients with normal and diseased aortic valves. An analysis of these central and peripheral pressure pulses is presented and their possible usefulness in the study of aortic valve lesions is discussed.

MATERIAL

Central aortic catheterizations were performed in 34 patients between 8 and 60 years of age. Three patients had normal aortic valves, 9 had "pure" aortic insufficiency, 9 had "pure" aortic stenosis, and 10 had combined aortic stenosis and insufficiency. Two patients with ruptured sinus of Valsalva aneurysm were studied because of the hemodynamic similarity of that lesion to aortic insufficiency. Normal sinus rhythm was present in 30 patients, while 4 had atrial fibrillation. Nine patients were operated upon for aortic stenosis, and Hufnagel valves were inserted in 4 others. In 6 of the 34 patients the heart was examined at necropsy.

METHODS

Patients were positioned supine on a fluoroscopic table and the right inguinal region cleansed and draped. The right femoral artery was palpated at the inguinal ligament and the overlying skin and subcutaneous tissues infiltrated with 1 per cent Xylocaine. A 13-gauge thin-walled needle was introduced percutaneously into the lumen of the artery. A No. 6 Cournand catheter, filled with heparinized saline, was passed into the aorta via the needle. Under fluoroscopic control its tip was positioned in the ascending aorta 1 to 2 cm. above the aortic valve. The Cournand catheter was connected to a Statham P-23-A pressure transducer and frequently irrigated with 1 to 2 c.c. of heparinized saline. In children and small adults a thin-walled 14-gauge needle and No. 5 Cournand catheter were used; the latter was connected to a P-23-D gauge. A No. 18 Cournand needle was then inserted into the contralateral femoral artery and connected to another P-23-A transducer by a rigid Saran connecting tube and adaptor. A multichannel cathode-ray photographic recording system was employed in 27 studies and a direct-writing recorder in the remainder. Central aortic and femoral artery pressures were then recorded simultaneously

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with Lead II of the electrocardiogram. Records were made at paper speeds of 25 and 50 or 75 mm. per second. Base lines for both pressures were at mid-thoracic levels. In 22 patients aortic valve gradients were measured by transbronchial left heart catheterization.[2]

Pressure measurements were averaged for a minimum of 5 beats in sinus rhythm, and for a minimum of 10 beats in atrial fibrillation. Analyses of time phase relationships of the pressure pulses were done from rapid paper-speed recordings in accordance with the definitions of Wiggers[3]; total ejection was measured from the onset of the anacrotic limb until 0.02 second before the incisura or dicrotic notch.[4]

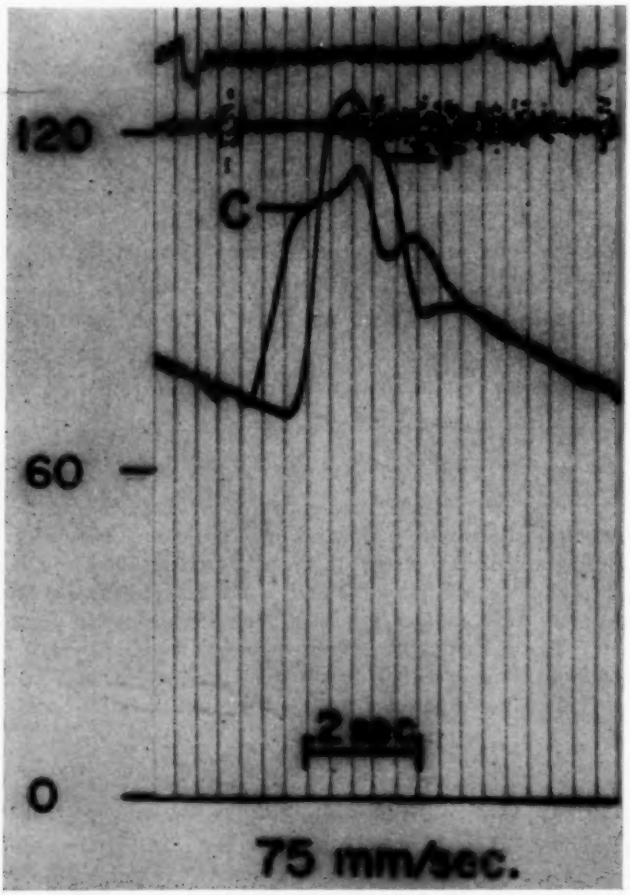

Fig. 1.—Simultaneously recorded central (*C*) and femoral (*F*) pressure pulses, ECG, and phonocardiogram, in a patient with a normal aortic valve. Scale in millimeters of mercury.

RESULTS AND ANALYSIS

Normal Aortic Valve.—With a normal aortic valve (Fig. 1) the contour of the central aortic pressure pulse showed an uninterrupted anacrotic rise to an initial shoulder or peak, followed by a more gradual rise to the second peak or point signifying the end of maximum ejection; a dip or slur between these two peaks was frequent. The level of the incisura averaged 63 per cent of the pulse pressure (measured from the level of the diastolic pressure) and was followed

by a well-formed wave. The femoral pressure pulse showed a steeper rise to a single peak (maximum ejection) and fell to a dicrotic notch which was lower than the incisura of the central pulse.

The first peak or shoulder of the central pressure pulse was reached in an average of 0.10 second after the onset of ejection; this averaged 35 per cent of total ejection. Maximum ejection in the femoral pressure pulse was reached in 0.12 second (anacrotic time); this averaged 43 per cent of total ejection time. Central aortic pulse pressures averaged 42 mm. Hg; femoral pulse pressures averaged 62 mm. Hg; and the ratio of femoral to central pulse pressure (F/C) averaged 1.48. The central-femoral step-up in systolic pressure averaged 18 mm. Hg, and the diastolic fall 3 mm. Hg.

Aortic Insufficiency.—Of the 9 patients in this group, all had mild-to-severe clinical aortic insufficiency. Eight had no systolic gradient across the aortic valve; one patient who was not catheterized had severe syphilitic aortic insufficiency with no clinical evidence of aortic stenosis.

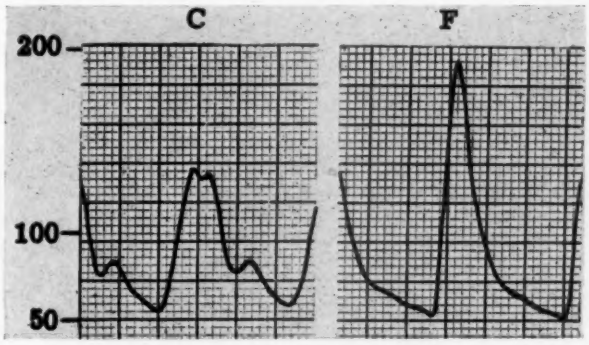

Fig. 2.—Cuttings from simultaneously recorded central (*C*) and femoral (*F*) pressure pulses in a patient with pure aortic insufficiency. Scale in millimeters of mercury. Paper speed 25 mm. per second.

The characteristic central aortic pressure pulse (Fig. 2) showed an uninterrupted rise to a sharp first peak; the second peak was higher, lower, or of equal height, and a dip between the two peaks was usually present. The height of the incisura averaged 41 per cent of the pulse pressure, and the wave which followed was prominent. The femoral pressure pulse rose rapidly to a peak; the catacrotic limb was collapsing, with a poorly defined dicrotic notch and wave. The first peak of the central pressure pulse was reached in an average of 0.15 second; this averaged 44 per cent of total ejection. Femoral anacrotic time averaged 0.11 second and 30 per cent of total ejection time. Central aortic pulse pressures averaged 71 mm. Hg, and the femoral 124 mm. Hg. The F/C ratio averaged 1.75, highest of all groups. Femoral systolic pressure exceeded central systolic pressure by an average of 44 mm. Hg; diastolic fall averaged 5 mm. Hg.

Aortic Stenosis.—In pure aortic stenosis the central aortic pressure pulse was characterized by one or more sharp vibrations beginning low on the anacrotic limb and a delayed first peak (pulsus tardus). Fig. 3 illustrates the

tracings in a patient with severe rheumatic aortic stenosis; at surgery the valve was rigid and densely calcified. The central tracing shows several early anacrotic vibrations followed by smaller vibrations continuing into diastole. The tracing is similar to those seen in severe experimental aortic stenosis.[5] The tracing shown in Fig. 4 was obtained in a patient with congenital aortic stenosis; at surgery, the aortic leaflets were found to be thin and mobile. The central aortic pressure pulse shows a single anacrotic interruption.

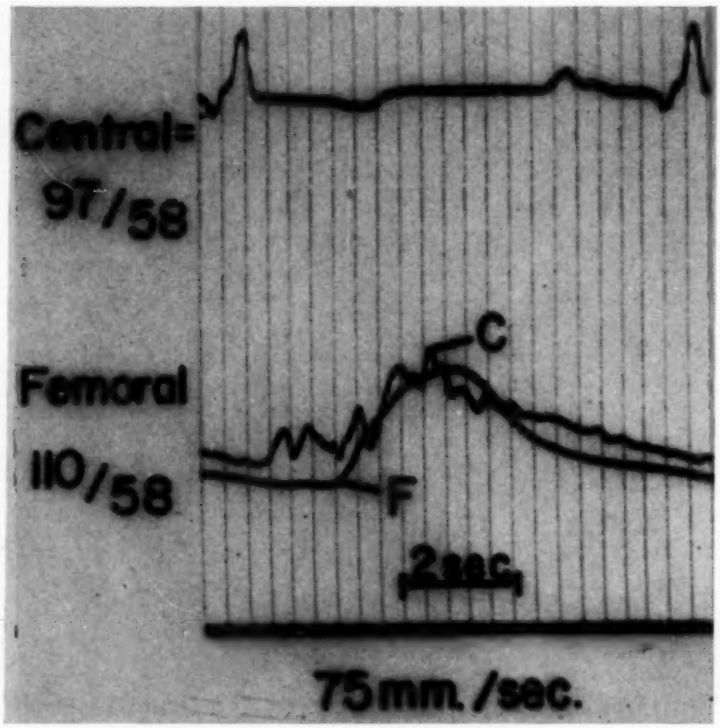

Fig. 3.—Simultaneously recorded central (*C*) and femoral (*F*) pressure pulses and ECG in a patient with pure aortic stenosis. Blood pressure in millimeters of mercury.

The level of the incisura in central tracings averaged 58 per cent of the pulse pressure, and the wave which followed was sometimes flatter than normal. The upstroke of the femoral pressure pulse was uninterrupted but slow, with a prolonged anacrotic time; the summit was usually rounded or flat (Figs. 3 and 4). Contrary to the experimental findings of Dow,[6] the central and femoral pressure pulses in aortic stenosis were different in both contour and magnitude.

The initial peak of the central pressure pulse was delayed to an average of 0.19 second, which was 56 per cent of total ejection time. Femoral anacrotic time averaged 0.20 second, and 61 per cent of total ejection. In the patients with valvular stenosis the central aortic pulse pressures averaged 35 mm. Hg. Femoral pulse pressures averaged 51 mm. Hg, and the F/C ratio averaged 1.46. The systolic pressure in the femoral artery exceeded central systolic pressure in every patient; the average increase was 13 mm. Hg. Diastolic pressure fell

an average of 3 mm. Hg. In one patient with subvalvular stenosis the central pulse pressure was 52 mm. Hg and femoral was 69 mm. Hg.

Aortic Stenosis and Insufficiency.—This group comprised 10 patients with combined stenosis and insufficiency. Fig. 5 illustrates tracings obtained in a patient with severe aortic insufficiency and a small degree of stenosis. The presence of an anacrotic vibration and a delayed first peak in the central pressure pulse was indicative of some aortic stenosis. The wide pulse pressure and low incisura indicated insufficiency.

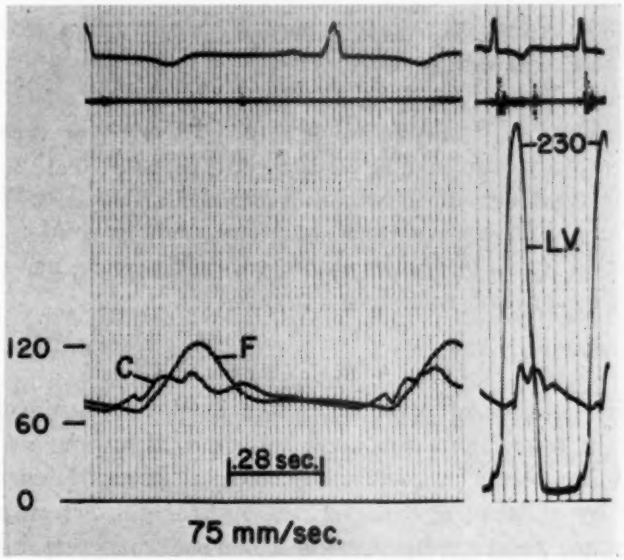

Fig. 4.—On the left are simultaneously recorded central (*C*) and femoral (*F*) pressure pulses and ECG in a patient with pure aortic stenosis. On the right are simultaneously recorded central aortic and left ventricular (*L. V.*) pressure pulses, ECG, and phonocardiogram in this patient demonstrating the large systolic gradient across the aortic valve. Scale in millimeters of mercury. Paper speeds 75 and 25 mm. per second, respectively.

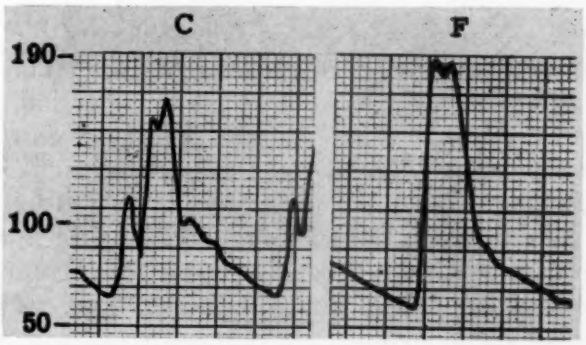

Fig. 5.—Cuttings from simultaneously recorded central (*C*) and femoral (*F*) pressure pulses in a patient with severe aortic insufficiency and a small degree of aortic stenosis. Scale in millimeters of mercury. Paper speed 25 mm. per second.

The central pulse pressures were wider than normal, and the level of the incisura averaged 35 per cent of the pulse pressure. The femoral pressure pulse was collapsing when the degree of aortic insufficiency was severe, less so when the findings of stenosis predominated. The summit was double peaked (bisferious), slurred, or rounded.

In these patients the first peak of the central pressure pulse was reached in an average of 0.19 second; this averaged 52 per cent of total ejection. Femoral anacrotic time averaged 0.16 second and 40 per cent of total ejection. Central aortic pulse pressures averaged 73 mm. Hg; femoral pulse pressures averaged 95 mm. Hg. The F/C ratio was 1.30, lowest of all groups. Femoral systolic pressure exceeded central systolic pressure by an average of 14 mm. Hg; the diastolic fall averaged 9 mm. Hg.

Sinus of Valsalva—Right Heart Fistula.—The 2 patients in this group each had a ruptured sinus of Valsalva aneurysm. In one, the fistula was between the base of the noncoronary cusp and the right atrium; in the other, the fistula was between the right coronary cusp and the right ventricle. The central and femoral pressure pulses were similar to those seen in mild-to-moderate aortic insufficiency. The levels of the incisurae were 36 and 28 per cent of the pulse pressures. The F/C ratios were 1.73 and 1.55.

DISCUSSION

Comparative studies of pressure pulses in the ascending aorta and a peripheral artery in man have not been reported although measurements have been made at other levels in the central arterial tree. Salens[7] obtained aortic arch pressures by passing a catheter via a brachial arteriotomy. Schnabel[8] studied pulse wave velocity by passing Peterson catheters into the ascending aorta through a 19-gauge needle inserted into the femoral artery. Kroeker and Wood[9] studied the differences between pressure pulses recorded in the descending thoracic aorta and the peripheral arteries in normal individuals. Radner[10] obtained aortic arch pressure pulses by suprasternal needle puncture, and Hansen[11] and Gordon[12] have used needle puncture at the operating table.

Grishman and associates,[13] Smith,[14] and Reinhold and associates[15] have studied indirect carotid artery pulses recorded from the body surface; they all stress the anacrotic vibrations as a qualitative measure of aortic stenosis.

In the femoral pressure pulses there was good correlation between the valve lesion and the ratio of time occupied by maximum ejection (anacrotic time) to total ejection. In the normal this ratio averaged 43 per cent. It was increased in aortic stenosis (61 per cent) and decreased in aortic insufficiency (30 per cent). In the central pressure pulse, on the other hand, there was no correlation between the valve lesion and the ratio of maximum ejection time to total ejection time. Good correlation, however, existed between valve function and the ratio of time to reach the first peak or shoulder to total ejection time. This latter ratio was consistently high in aortic stenosis (56 per cent), and low with normal aortic valves (35 per cent).

Studies in dogs[1] revealed that the femoral pulse pressure was approximately double the central pulse pressure (F/C averaged 2.2) both in normal dogs and

in dogs with aortic insufficiency. Dow[6] demonstrated a reduction in this pulse pressure increase in dogs with acute aortic stenosis; he felt that aortic stenosis obliterated the normally present aortic standing waves. In contrast, our data in patients indicate a near-normal step-up in pulse pressure (F/C pulse pressure ratio of 1.46) as well as major alterations of the pressure pulse contours in aortic stenosis (Figs. 3 and 4). The highest F/C ratios in this study occurred in "pure" aortic insufficiency (1.75); the lowest in combined stenosis and insufficiency (1.30).

Analysis of the contour of the central pressure pulse also proved helpful. An anacrotic interruption always indicated some aortic stenosis; other parameters—pulse pressure, ratio of the first peak or shoulder to total ejection time, level of the incisura, and the F/C pulse pressure ratio—were of value in estimating the severity of stenosis and the degree, if any, of insufficiency which accompanied it.

SUMMARY AND CONCLUSIONS

1. Pressure pulses were recorded simultaneously from the ascending aorta and femoral artery in 34 unanesthetized patients with normal and diseased aortic valves. These pressure pulses have been compared and analyzed qualitatively and quantitatively.

2. Central aortic pulse pressures and femoral/central pulse pressure ratios averaged 42 mm. Hg and 1.48 with normal aortic valves, 71 mm. Hg and 1.75 in "pure" aortic insufficiency, 35 mm. Hg and 1.46 in "pure" aortic stenosis, and 73 mm. Hg and 1.30 in combined aortic stenosis and insufficiency.

3. The level of the incisura above the diastolic pressure averaged 63 per cent of the pulse pressure with normal aortic valves, 41 per cent in aortic insufficiency, 58 per cent in aortic stenosis, and 35 per cent in combined stenosis and insufficiency.

4. In the femoral pressure pulse there was good correlation between the valve lesion and the ratio of the time occupied by maximum ejection to total ejection. This ratio was increased in aortic stenosis (61 per cent) and decreased in aortic insufficiency (30 per cent).

5. In the central aortic pressure pulses the ratio of time to reach the first peak or shoulder to total ejection time was high in aortic stenosis (56 per cent) and low with normal aortic valves (35 per cent).

6. Femoral systolic pressure exceeded central aortic systolic pressure by an average of 18 mm. Hg with normal aortic valves, 13 mm. Hg in aortic stenosis, and 44 mm. Hg in aortic insufficiency. Systolic step-up was relatively small (average 14 mm. Hg) in combined aortic stenosis and insufficiency.

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Primary Pulmonary Systolic Hypertension Associated With Aneurysm of Pulmonary Artery

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This report presents the clinical and laboratory details in an unusual instance of primary pulmonary hypertension. This patient differs from the usual one with this disease in that the elevation of the pulmonary pressure is limited to the systolic pressure, there is no significant thickening of the pulmonary arterioles, and there has been no evidence of progression during a 3-year period of observation.

CASE REPORT

B. M., an 11-year-old white girl, was first seen in this hospital on Jan. 12, 1954, having been referred to the Contagion Division because of an acute febrile illness thought to represent encephalitis of infectious origin. A harsh systolic murmur unaccompanied by a thrill, which had first been noted over the entire precordium at the age of 3 months, had not changed in character over the years. The child was rather gracile (57 inches tall, 72 pounds in weight), had walked at a normal age, had not had an unusual number of respiratory infections, and was said to have had mild exertional dyspnea and fatigability quantitatively unchanged since early childhood. A chest film had never been obtained.

Physical examination on admission revealed an acutely ill, oriented child with a temperature of 40.2°C. Petechiae were noted on the arms, legs, and abdomen. There was no cyanosis. The heart was not enlarged and no thrills were felt. There was questionably increased activity over the left parasternal area. A moderately loud and harsh holosystolic murmur of medium pitch was heard best over the second, third, and fourth right parasternal areas, but was also audible over the entire thorax and was transmitted into both carotid arteries. The murmur obliterated the aortic closure sound but not the second pulmonic sound. No diastolic murmur was present. A soft, blowing systolic murmur was also heard at the apex. The characteristics of these murmurs did not change during this hospitalization. The lungs were clinically normal, as were the neurological findings, two spinal fluid examinations, and the urine. The white blood cell count was elevated with an increase in the polymorphonuclear leukocytes. An hemolytic, coagulase negative

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Staphylococcus aureus was grown from several blood cultures obtained on admission; a diagnosis of staphylococcal bacteremia was made, and appropriate chemotherapy was started on the third hospital day.

On the sixth hospital day dullness to percussion and râles were noted for the first time over the right middle and lower lobes, and a chest roentgenogram confirmed the diagnosis of pneumonia. Recovery was slow but complete and the temperature, which became normal by the fortieth hospital day, remained normal thereafter. Several right thoracenteses, with aspiration of straw-colored fluid, smear positive for staphylococci, were necessary during this illness.

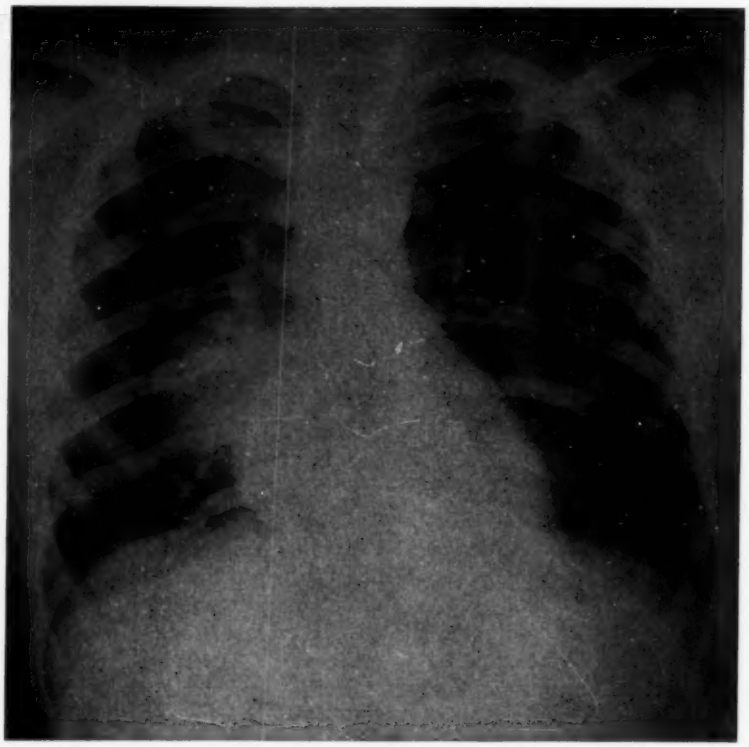

Fig. 1.—Chest roentgenogram showing right parahilar mass.

As the pneumonic process gradually cleared roentgenographically, a rounded right parahilar density, not seen in the first films because of the consolidation and effusion present, became well delineated (Fig. 1). The nature of this lesion, thought to represent either an encapsulated effusion or a bronchogenic cyst, was not elucidated. The patient was discharged on the fiftieth hospital day with the additional diagnosis of congenital heart disease of unknown type. It was believed that an unrecognized pneumonia had been present on admission, and that there was no definitive evidence that the patient had had bacterial endocarditis.

The patient was readmitted 2 weeks later for further evaluation of the cardiac lesion and the parahilar mass which had remained unchanged in appearance. On bronchoscopy the orifices of the main right middle and lower lobe bronchi were normal, with external compression of the right intermediate bronchus. A saccular aneurysm of a branch of the right pulmonary artery was now suspected. Since two separate surgical procedures were contemplated, it was thought best to deal first with the parahilar mass, delaying further diagnostic cardiac procedures to a later date.

On thoracotomy, by G. H. A. Clowes, M.D., a large, blue, pulsating mass, the site of a marked systolic thrill, was found in the fissure between the middle and lower lobes. There was also a thrill in the artery leading to the apical segments of the right upper lobe. Compression of the

main right pulmonary artery proximal to the mass obliterated both thrills. Because of severe erosion of the bronchus to the lower lobe, the artery was ligated proximal to the aneurysm and a right lower lobectomy was performed. Although a thrill remained in the artery to the upper lobe, a second aneurysm could not be identified.

The loud, harsh, right parasternal murmur now became much less loud, and the closure sound in the second right parasternal area was clearly audible. The soft, blowing apical systolic murmur was unchanged. Recovery was uneventful and the patient was discharged on the seventeenth postoperative day (April 11, 1954).

The gross specimen consisted of a pyramidal portion of lung measuring 8 cm. along the base and 10 cm. in height. The pleural surfaces were smooth and glistening and the lung was normally crepitant. At the hilus, the pulmonary artery ostium measured 0.3 cm. in diameter. Immediately distal to this point the artery widened into a saccular aneurysm that measured 4.5 cm. in diameter.

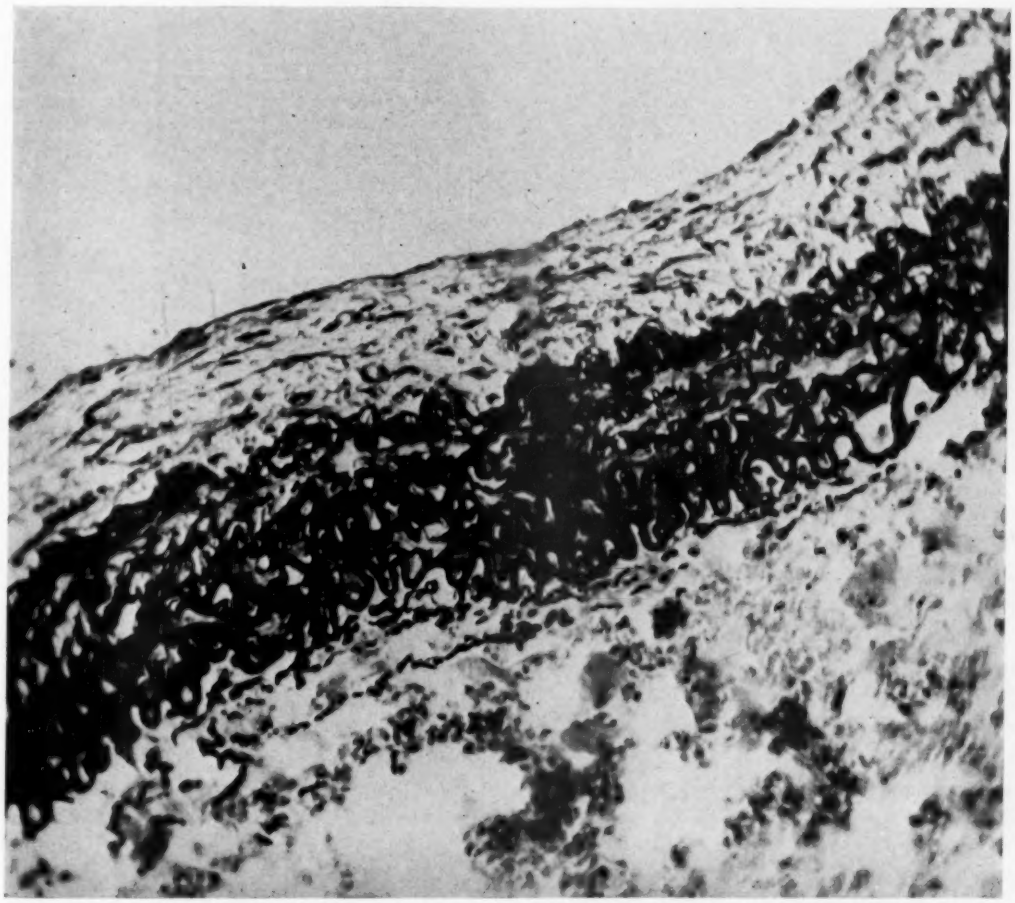

Fig. 2.—Longitudinal section of one of the larger pulmonary arteries in the resected right lower lobe, showing moderate intimal thickening. (Verhoeff elastic stain, ×360; reduced ⅓.)

The lining was smooth and glistening and 5 separate outflow tracts were identified. No communication with the venous system could be found. The other branches of the pulmonary artery, the pulmonary veins, and the bronchi were not remarkable.

Microscopic sections of the aneurysm showed a thickened, irregular wall. The intimal surface contained thin patches of fibrinoid material, which in some areas were partially covered by endothelium. No division could be made between intima, media, and adventitia, since the wall was

made up of scattered, irregular, stellate cells within a hyalinized matrix. Masson's stain revealed that most of the wall was fibrous connective tissue. Only a few small fragments of distorted elastic tissue could be identified in sections stained by Verhoeff's method. The surrounding pulmonary parenchyma was slightly atelectatic, and the alveoli contained a large amount of fresh blood, some fibrin, and a moderate number of polymorphonuclear neutrophils. However, the interalveolar septa showed no significant thickening or fibrosis. The pulmonary parenchyma away from the aneurysm showed large patches of edema, but no inflammatory changes and no areas of fibrosis.

Microscopic examination of the larger branches of the pulmonary artery showed moderate fibrous intimal thickening (Fig. 2) in a few segments, but normal walls in the majority. The small arteries (150 to 250 μ diameter) were also normal in thickness for the most part, although a few showed slight fibrous intimal thickening. In one vessel of 200 μ outside diameter the lumen was narrowed to about one third the original diameter. However, the over-all involvement was not extensive or marked enough to have produced any significant obstruction to blood flow.

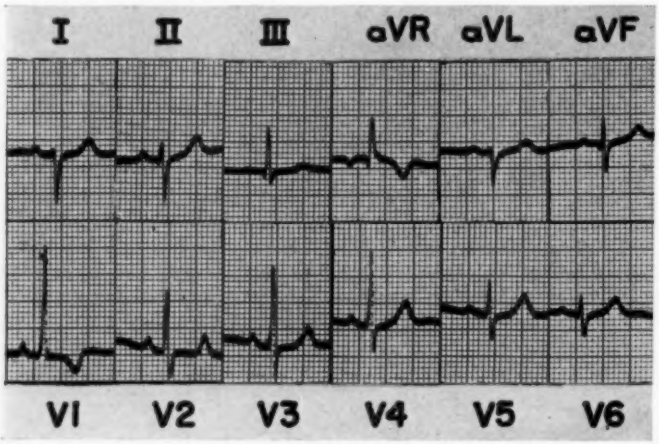

Fig. 3.—Electrocardiogram obtained prior to lobectomy, and interpreted as showing right ventricular hypertrophy. There was no change in these tracings during the 3½ years of observation.

The pulmonary arterioles were not thickened. The lumen-to-wall ratio of the arterioles was measured by a method previously described,[4] and the value was found to be 5.5. This is within the range of 4.4 to 7.6 that was found previously in a normal control group which had no evidence of pulmonary or cardiac disease.

The patient was seen again on Sept. 7, 1954, for cardiac catheterization. The physical findings were unchanged. Except for the slower heart rate, the electrocardiogram (Fig. 3) was unchanged from that obtained on the second day of the first admission in January, 1954. Cardiac fluoroscopy showed a normal silhouette with no enlargement of the heart chambers. A minimal upper dorsal scoliosis was likewise unchanged (Fig. 4).

Cardiac catheterization revealed a pulmonary artery pressure of 90/15 mm. Hg. Complete diagnostic scanning of the right side of the heart showed no evidence of right-sided obstruction or intracardiac shunt (Table I).

The patient was not seen again until she was readmitted for follow-up study on May 1, 1957, almost 3 years later, at the age of 15 years. She had grown in height to 60 inches, and in weight to 96 pounds. The slight upper dorsal scoliosis had progressed to a rather severe kyphorotoscoliosis, with an increase in angulation from 18 to 44 degrees (Fig. 5). There was still minimal exertional dyspnea. The electrocardiogram was identical with those obtained in 1954. The clinical cardiac findings were unchanged, and the heart was likewise considered to be unchanged on fluoroscopic examination. Cardiac catheterization was repeated and revealed findings similar to those

Fig. 4.

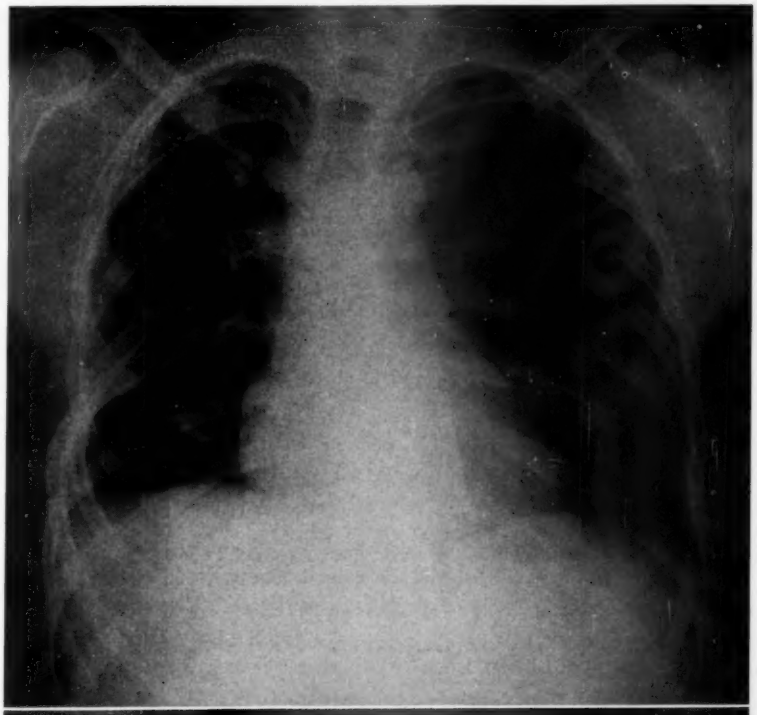

Fig. 5.

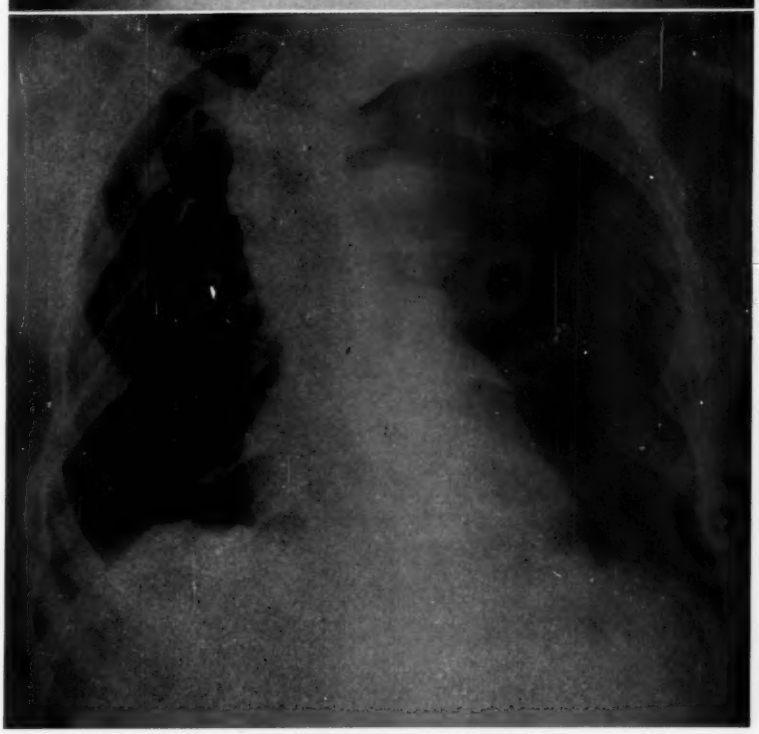

Fig. 4.—Chest roentgenogram—two months following right lower lobectomy.
Fig. 5.—Chest roentgenogram—three years following lobectomy.

obtained in September, 1954, with a marked pulmonary systolic hypertension and normal pulmonary diastolic pressure (Table I; Fig. 6). Pulmonary function studies were consistent with those described by Fishman[9] for adults with kyphorotoscoliosis, in whom respiratory dysfunction appears to be mainly the result of mechanical restriction of the thoracic cage.

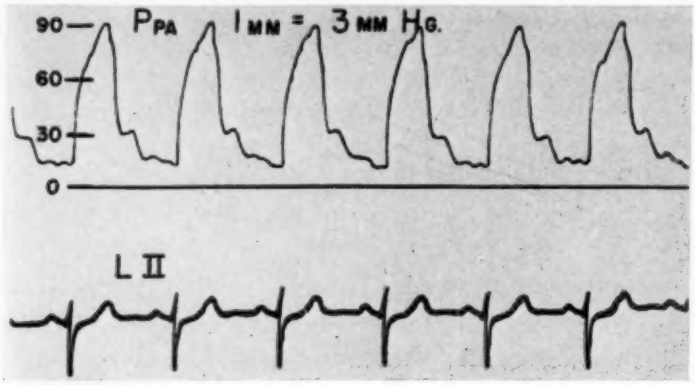

Fig. 6.—Pulmonary artery pressure pulses recorded during second catheterization (May 6, 1957). Note the rapid systolic descent and normal end-diastolic pressure.

TABLE I. DATA OBTAINED AT CARDIAC CATHETERIZATION 4 MONTHS, AND AGAIN 3 YEARS, AFTER RIGHT LOWER LOBECTOMY AND ANEURYSMECTOMY

	SEPT. 7, 1954 (REST)	MAY 6, 1957 (REST)	(EXERCISE)*
P_{RA}	7/3 (5.2)	7/4 (4.9)	
P_{RV}	95/7 (38.0)	94/7 (35.1)	
P_{PA}	90/15 (42.7)	90/10 (36.6)	103/10 (43.7)
P_{WP}	(9.3)	(7.1)	
P_{BA}	87/65 (75.2)	120/78 (92.5)	136/85 (96.4)
Per cent arterial saturation	95.2	93.2	93.2
Hemoglobin	13.2 Gm.	12.3 Gm.	——
C. I.	——	2.08 L.	2.63 L.
PU. T. R.	——	1,052 c. g. s.	992 c. g. s.
P. V. R.	——	848 c. g. s.	——

*After 12 minutes of steady state exercise at 850 foot pounds per minute.

P_{RA}, P_{RV}, P_{PA}, P_{WP}, P_{BA} = right atrial, ventricular, pulmonary artery, wedge, and brachial artery pressures in mm. Hg (mean pressures in parentheses). C.I. = cardiac index (liters/square meter/minute). PU.T.R. and P.V.R. = total pulmonary and pulmonary vascular resistances (dynes/cm.$^{-5}$).

Note the normal response of pulmonary artery pressure and total pulmonary resistance to exercise, despite the marked resting elevations of systolic pressure and calculated resistance.[15] Complete scanning for oxygen saturations in the venae cavae and the right side of the heart revealed no evidence of shunt on either occasion. These data are omitted.

DISCUSSION

This case differs in three respects from other cases of "idiopathic primary pulmonary hypertension" that have been reported since the advent of cardiac catheterization:

1. The diastolic pressure in the pulmonary artery is normal. Among 29 cases of primary pulmonary hypertension collected at random from the litera-

ture[2,3,5-7,9-11,16,17] the lowest recorded diastolic pressure has been 30 mm. Hg, excepting 2 cases with 25 and 29 mm. Hg, respectively. In 5 proved cases (postmortem, surgery) in our laboratory[14] the lowest single resting pulmonary diastolic pressure has been 30 mm. Hg.

2. There has been no evidence of progression. Although an occasional exception has been reported,[2,12] in most patients with primary pulmonary hypertension the disease is rapidly progressive, and death ensues within a few months to 4 or 5 years after the onset of symptoms.

3. The small muscular arteries and arterioles in the surgical specimen were essentially normal, the lesions being limited to the larger arteries. Although it was difficult to evaluate the significance of the vascular lesions, it is possible that the intimal thickening of the larger arteries was enough to cause some decrease in their distensibility. Dresdale, Schultz and Michtom[7] have collected cases formerly reported as "idiopathic hypertrophy of the right ventricle" in which no lesions could be found in the pulmonary vascular bed. The evidence that such cases represent the end result of a functional primary pulmonary "diastolic" hypertension does not appear conclusive. It is striking that in all well-documented cases reported in the literature, with combined catheterization and postmortem data, there has always been a severe degree of arteriolar disease.

A case similar to the one herein presented was reported by MacKenzie and Clagett.[13] They dealt with an asymptomatic 28-year-old dentist who had a murmur known to have been present since birth. A left upper lobectomy was done for the removal of a fusiform aneurysm of the pulmonary artery to that lobe. During cardiac catheterization performed prior to surgery, the pulmonary artery pressure was found to be 60/10 mm. Hg. The authors commented on this unusual pressure pattern, noted that it had never been encountered previously in their laboratory, and ascribed this hemodynamic finding to either decreased arterial distensibility or decreased systolic runoff. Unfortunately, a detailed presentation of the pathologic findings in the pulmonary vessels other than those of the aneurysm is not available.

A free pulmonic regurgitation is known to produce a wide pulse pressure in the pulmonary artery. This is unlikely to be a factor in our patient since at no time has a diastolic murmur been heard. Patients with kyphoscoliosis may have pulmonary hypertension. The role of this malformation is of no consequence here, since pulmonary hypertension existed at a time when the deformity was barely noticeable, and has not changed with the severe progression of the abnormal spinal curvature.

It is of interest that in both our case and that of MacKenzie and Clagett a pulmonary artery aneurysm was found. The pathologic evidence in both supported a noninflammatory etiology of the aneurysms, although in neither case can it be stated unequivocally that they were congenital, and not acquired some time after birth as the result of a chronic increase in systolic pressure. It is likewise possible that the aneurysm in the present case may have been mycotic in origin, despite the lack of microscopic evidence for inflammation. As more cases are studied, however, the association of pulmonary artery aneurysms, normal pulmonary arterioles, and primary systolic pulmonary hypertension, in the absence of associated cardiac shunting defects, may become an established entity separate from that of idiopathic primary pulmonary hypertension.

Dresdale and associates[7] have drawn a clinical analogy between primary pulmonary hypertension and essential peripheral hypertension. On the basis of the findings in the present case, one may make a comparison between *primary systolic pulmonary hypertension* and peripheral systolic hypertension. Although one cannot predict that our patient, as well as MacKenzie and Clagett's, may not, in time, develop arteriolar lesions and diastolic hypertension, the prognosis would appear to be considerably better in the two subjects under consideration than in the usual individual with primary pulmonary hypertension. It is also possible that the occasional persons reported to have had an unexpected longevity[2,12] with the disease complex presently termed "idiopathic primary pulmonary hypertension" may actually represent instances of primary systolic hypertension.

SUMMARY

We have reported the case of a 15-year-old white girl in whom a right lower lobectomy was done because of an aneurysm of the pulmonary artery. The pathologic specimen showed essentially normal pulmonary arterioles and only slight intimal hyperplasia of the larger pulmonary arteries. Cardiac catheterization revealed an unusual pattern of marked systolic hypertension with a normal diastolic pressure. When repeated 3 years later, the catheterization data were unchanged and there was no clinical, roentgenologic, or electrocardiographic evidence of progression of the disease. One similar case has been reported in the literature.

It is suggested that primary systolic pulmonary hypertension may be an entity different from primary pulmonary diastolic hypertension, and may have a considerably better prognosis.

Thorough investigation of patients with pulmonary artery aneurysms may reveal a significant association of the latter with pulmonary systolic hypertension, with a normal diastolic pressure, and with normal pulmonary arterioles.

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The Successful Correction of Atrioseptal Defects Combined With Transposition of the Superior Vena Cava and Aberrant Pulmonary Veins, Utilizing the Pump Oxygenator

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Total cardiopulmonary bypass, utilizing the pump oxygenator, has provided the means to correct lesions within the heart under direct vision. We have operated upon 6 patients with interatrial septal defects using this technique. One of these cases is reported now because of the unusual nature of the lesions and the surgical technique utilized for their successful repair.

The surgical repair of atrioseptal defects has become the accepted method of treatment. It is our belief that these defects should be repaired by open cardiotomy. A survey of the literature discloses no other case of atrioseptal defect associated with pulmonary veins transposed into a superior vena cava, which itself was transposed into the left atrium. These lesions proved to be completely correctable by means of open intracardiac repair. It is unlikely that repair could have been effected by use of any other technique. Although palpation of the atrium indicated only one huge defect, exploration of the atrium under direct vision revealed a second, dime-sized defect. This latter finding undoubtedly accounts for residual arterialization of right atrial blood, following closure of septal defects with blind closed techniques.

CASE REPORT

G. M., a 45-year-old white woman, was admitted to the hospital on March 8, 1957, for the third time, complaining of exertional dyspnea, and easy fatigability. The patient was known to have had a murmur without cyanosis since early childhood. Following the birth of her first child 21 years before, she had noted the onset of easy fatigability. Five years prior to admission in March 1957, she had developed moderate exertional dyspnea, which was progressive up to the time of admission. In 1954, digitalization was instituted because of auricular flutter fibrillation, which also persisted to the time of admission in 1957. Five months prior to this last admission, she developed congestive heart failure, with ankle edema and hepatomegaly.

Physical examination revealed an acyanotic, well-developed, white woman in no acute distress. The heart was enlarged to the left by percussion. There was a harsh Grade 3 systolic mur-

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mur audible over the precordium, with maximal intensity over the pulmonic area. The pulmonic second sound was markedly accentuated, snapping, and louder than the aortic second sound. The rhythm was grossly irregular, with a ventricular rate of 80. The blood pressure was 125/80 mm. Hg. The liver was palpable 2 fingerbreadths below the costal margin. There was 1+ pretibial edema. The remainder of the physical examination was noncontributory.

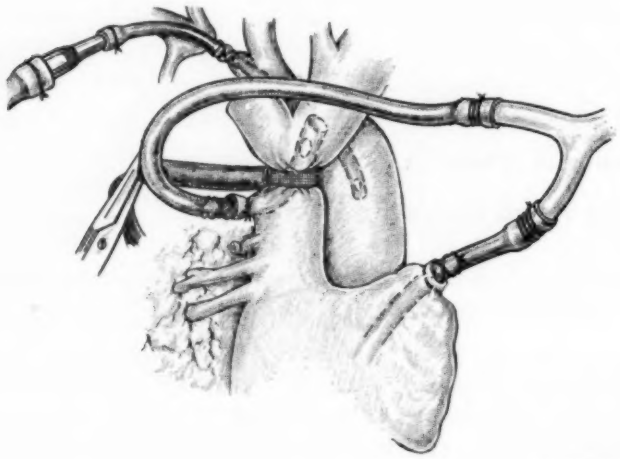

Fig. 1.

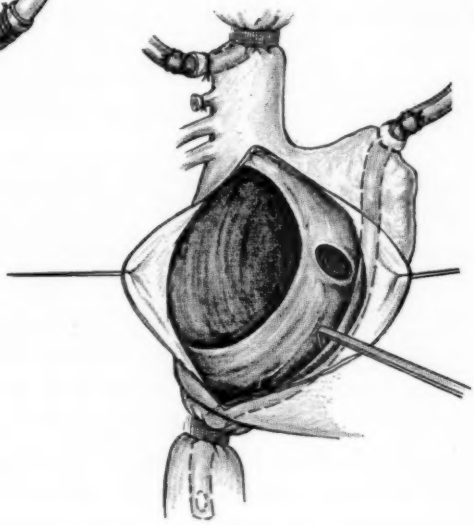

Fig. 2.

Fig. 1.—Cardiopulmonary bypass was effected by cannulating the superior and inferior venae cavae. The superior vena cava was cannulated through the apical segmental pulmonary vein; the inferior cava through the auricular appendage. Blood was returned through a catheter in the right subclavian artery. The right upper and middle lobe pulmonary veins were transposed into the superior vena cava, which itself was transposed into the left atrium.

Fig. 2.—Upon opening the atrium, two atrioseptal defects were found. One large defect, measuring 5 cm. in diameter, was found superiorly and posteriorly. This defect was connected by a rim of tissue superiorly, anteriorly, and inferiorly. There was no rim posteriorly. The superior vena cava emptied into the left atrium, to the left of the atrioseptal defect. A second, dime-sized defect was found anterior to the larger one.

Cardiac fluoroscopy and roentgenograms of the thorax revealed the heart to be greatly enlarged in its transverse diameter. The pulmonary artery segment was markedly prominent and pulsatile, and the pulmonary vascular markings were greatly accentuated. In the right anterior oblique there was considerable anterior encroachment, indicating enlargement of the outflow tract of the right ventricle. The left atrium was not enlarged. Angiocardiography confirmed the right-sided enlargement of the heart and pulmonary artery.

The electrocardiogram revealed atrial fibrillation and right axis deviation. There was an absence of a terminal R wave in aV_R, but there was an rsR′ pattern in V_1, and a deep S wave in V_6. Routine laboratory work was within normal limits.

Cardiac catheterization was performed on Jan. 10, 1957, and revealed arterialization of the right atrial blood. The femoral arterial blood oxygen saturation was only 88 per cent. The pres-

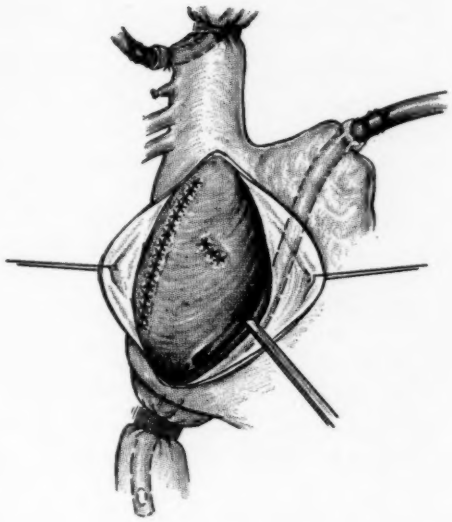

Fig. 3.

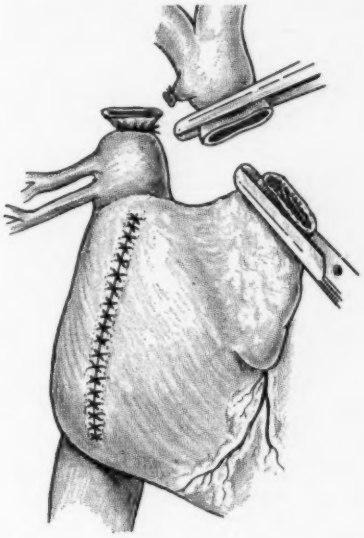

Fig. 4.

Fig. 3.—Both atrioseptal defects were closed with interrupted figure-of-eight sutures.

Fig. 4.—The superior vena cava was transected above the level of the aberrant pulmonary veins, and the proximal end was anastomosed with the right auricular appendage. This maneuver permitted the aberrant pulmonary veins to drain into the stump of the superior vena cava, and thence into the left atrium. Drainage of the superior vena cava was redirected into the right atrium.

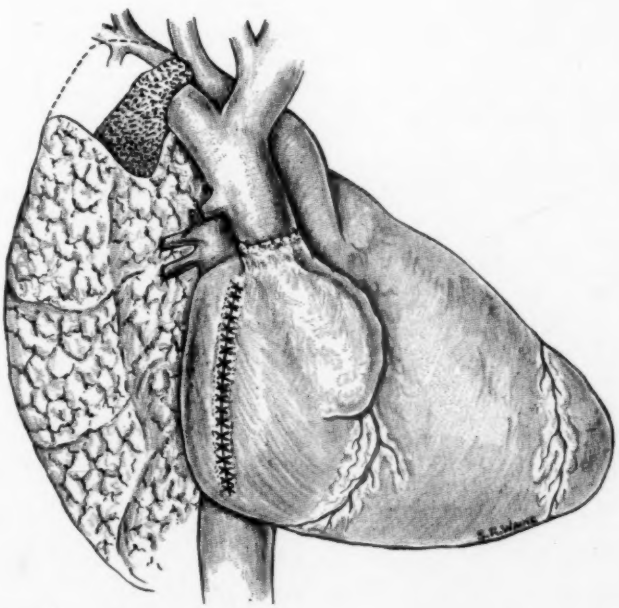

Fig. 5.—Following ligation of the apical segmental vein, the apical segment developed a venous infarct. Accordingly, an apical segmental resection was performed. In this fashion, complete correction of all lesions was accomplished.

sures revealed a mild pulmonary and right ventricular hypertension. The results (Table I) were compatible with an interatrial septal defect, with a significant left-to-right, and a small right-to-left, shunt.

Operative Report.—On March 14, 1957, under total cardiopulmonary bypass, operation was undertaken. Two atrioseptal defects were present. The right upper and middle lobe veins were found transposed into the superior vena cava, which itself was transposed into the left atrium (Fig. 1). The right atrium was markedly dilated. The veins from the right middle lobe joined together and entered the superior vena cava 1 cm. above its entrance into the heart. The anterior and posterior segmental veins of the right upper lobe joined together and drained into the superior vena cava immediately above the middle lobe vein. The apical segmental vein entered the superior vena cava singly, approximately 5 cm. above the other pulmonary veins.

On digital exploration, one large atrioseptal defect measuring 5 cm. in diameter was encountered superiorly and posteriorly. The superior vena cava emptied into the left atrium, to the left of the atrioseptal defect. When the atrium was opened, a second, dime-sized defect was found anterior to the larger one (Fig. 2).

Under total cardiopulmonary bypass, the right atrium was opened, and both defects closed with interrupted figure-of-eight, 2-0 atraumatic Deknatel* sutures (Fig. 3). As the atrium was allowed to fill with blood, the incision in its wall was closed with a continuous 3-0 atraumatic Deknatel suture. With closure of the atrioseptal defect, the superior vena cava with its transposed pulmonary veins emptied into the left atrium, which no longer communicated with the right side. On completion of the cardiopulmonary bypass, the superior vena cava was transected above the level of the transposed pulmonary veins, and the upper end was anastomosed with the right auricular appendage (Fig. 4). This maneuver left uninterrupted the drainage of the upper and middle lobe pulmonary veins into the stump of the superior vena cava, and thence into the left atrium. Drainage of the upper portion of the superior vena cava, on the other hand, had been redirected into the right atrium. The period of total superior vena caval occlusion was approximately 17 minutes. Because the apical segmental pulmonary vein could not be anastomosed to the main upper pulmonary vein, it was ligated. On completion of the retransposition of the superior vena cava, the apical segment of the upper lobe was edematous and boggy, and sanguinous material was aspirated from the endotracheal tube. Accordingly, an apical segmental resection was performed (Fig. 5).

Upon termination of the procedure, there were scattered petechiae over the patient's face, chest, and upper extremities, which were also intensely cyanotic. However, the cyanosis was noted

TABLE I. RESULTS OF CARDIAC CATHETERIZATION

SITE	O_2 CONTENT (VOL. %)	PRESSURE (MM. Hg)
RPA	18.2	35/13 (21)*
MPA	18.1	30/12 (20)
MPA	——	40/13
MPA	18.1	35/18
RV (outflow)	17.9	39/−2 (24)
RV (mid)	17.6	39/−1 (22)
RA	17.2	(8)
SVC	14.7	
Femoral Artery	17.8	
Capacity	20.6	
Saturation	88%	

*The figures in parentheses represent mean pressures.

*Prepared by J. A. Deknatel & Son, Inc., Queens Village, Long Island, N.Y.

to be subsiding within an hour after completion of the procedure. The face and lids were edematous, and there were hemorrhages in the conjunctivae.

Postoperatively.—The patient was moderately disoriented for the first 4 days postoperatively, but gradually recovered. The urinary output on the first 2 postoperative days was 500 and 900 c.c., respectively, with a specific gravity of 1.004. The electrolytes were normal. On the third postoperative day, the urinary output rose to 3,000 c.c. with a specific gravity of 1.006. It rose to 3,500 c.c. on the fourth, fifth, and sixth postoperative days, and required massive parenteral replacement therapy. The urine output simulated that of a patient with diabetes insipidus. It was felt that this state may have resulted from petechial hemorrhages or edema in the pituitary at the time of surgery. The polyuria subsided spontaneously. The postoperative course, thereafter, was uneventful.

At the present time, the patient has resumed normal activity, and performs her household duties without dyspnea or fatigability. The systolic murmur has disappeared, and the second pulmonic sound is no longer accentuated. Atrial fibrillation persists, and the ventricular rate is controlled with Digoxin.

DISCUSSION

Transposition of the right pulmonary veins into the right atrium is usually associated with interatrial septal defects, and has been previously described by Lewis,[4] Bailey,[5] and Swan and associates.[6]

Less frequently, however, the right-sided pulmonary veins may drain into the superior vena cava. Lewis[4] has described this anomalous pulmonary venous drainage of the right superior and middle pulmonary veins as being associated with high atrioseptal defects which occur above the fossa ovalis. These defects characteristically lack complete margins superiorly and posteriorly. Embryologically, such defects have been attributed to an abnormal entrance of the superior vena cava into both the right and left atria, rather than to a defect of the septum.[1-3] Edwards and Helmholz[7] suggest that this lesion may be due to a persistence of a venous connection between the splanchnic plexus and the cardinal system of veins. The inferior vena cava has been similarly reported to enter into the left atrium, to the left of an interatrial defect, as in a patient we recently explored. This may be attributable to an abnormal prominence of the valve of the inferior cava, which seems to form an inferior rim to the low foramen ovale type of defect.

Complete correction of the combined defects in our patient could not have been undertaken without the direct approach afforded by use of the pump oxygenator. Only with the atrium widely opened could both defects be closed successfully. Following closure of the defects, the flow of blood from the superior vena cava, with its transposed pulmonary veins, was directed into the left atrium. Transection of the superior vena cava above the entrance of the pulmonary veins permitted them to empty into the left atrium by way of the proximal vena caval stump, thereby correcting the pulmonary venous cardiac return. Implantation of the superior vena cava into the right auricular appendage served to reconstitute the normal systemic venous return. Since the pulmonary vein which drained the apical segment of the right upper lobe could not be transplanted, and since its ligation initiated a pulmonary venous infarct, an apical segmental resection was performed. This triple surgical procedure completely corrected the intracardiac pathology as well as the abnormalities of venous return in this patient.

SUMMARY

1. A case is reported of two atrioseptal defects, associated with transposition of the superior vena cava into the left atrium, and anomalous return of the right upper and middle lobe veins.

2. Complete correction was accomplished, utilizing the pump oxygenator.

3. The superior vena cava was redirected into the right atrium, and the aberrant pulmonary veins into the left atrium. An apical segmental resection completed the operative procedure.

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The Holistic Approach to Angina Pectoris

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INTRODUCTION

Therapy of angina pectoris has been based mainly upon the use of vasodilators, particularly nitrate derivatives, although results have been frequently disappointing. In recent years, surgical measures have been devised, aimed at increasing myocardial blood flow, thus alleviating the pathologic physiology of the syndrome. Surgeons have made enthusiastic claims for these procedures and have placed the cardiologist somewhat on the defensive in the medical treatment of angina pectoris and other forms of arteriosclerotic heart disease.

Having observed a group of anginal patients for some time, the author has come to realize that patients with angina, although undoubtedly suffering from organic changes in the coronary arteries, present a therapeutic challenge that cannot be met by advocating any one particular procedure. Indeed, they represent a management problem that requires the physician to utilize all his faculties in the treatment of this symptom.

Angina pectoris is the result of many factors, both endogenous and exogenous. Atheromatous changes, exercise, digestion, emotional conflicts all participate in the causation of substernal pain. As a result, an attempt has been made to pay less attention to the symptom and to treat the patient as a whole. This plan of therapy consists of definite facets. First, a careful evaluation of the cardiac status has been made, with a view toward determining what the patient can and cannot do. Secondly, since many patients are terribly frightened of the pain, and the symbolism of the pain, e.g., sudden death or severe heart disease, reassurance is given that angina pectoris is compatible with both a long and productive life. Thirdly, attempts have been made to solve domestic and business problems with the patient so that emotional tension may be lessened. Finally, the use of tranquilizers, particularly meprobamate, has been found most useful.

The patients have been seen fairly frequently, at least once monthly, in order to perpetuate the confidence many have attained. As a result, reliance has been placed less and less on vasodilating drugs and more and more on reassurance and reconstruction of the patients' confidence.

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The purpose of this paper is to report the results with this scheme of treatment in 25 patients, and to discuss, on the basis of these results, some of the more controversial aspects of therapy in angina pectoris. This multidimensional approach to the problem has been pursued for at least 6 months. Comparisons are made between this more recent period and the status of the patients when they were treated solely with vasodilators. Since drug evaluation alone was not the sole purpose of this study, the "double-blind technique" was not used. Patients were not aware that they might be the subject of a paper. If they asked, they were told that a tranquilizer was being added to, or substituted for, the nitrate preparation they had been taking previously.

CLINICAL MATERIAL AND RESULTS

As Table I illustrates, 25 patients were studied. There were 18 men and 7 women. The youngest patient was 43, the eldest 70, with an average age of 53 years. The etiological factors were, as might be expected, arteriosclerotic heart disease in 16; hypertensive cardiovascular disease, which also implies coronary atherosclerosis, in 8; and rheumatic aortic valvular disease in 1.

The close connection between angina pectoris and coronary atherosclerosis is vividly demonstrated, for only 1 patient had a normal electrocardiogram when seen initially. Eleven of the patients had myocardial infarction as the initial episode of arteriosclerotic heart disease. The group has been followed on the average of 3 years and 10 months. The patient who has been followed the longest

TABLE I. SUMMARY OF CLINICAL MATERIAL

Number of Patients		*Anginal Episodes Daily*	
Total	25	Before therapy	7
Men	18	Greatest number	12
Women	7	Least number	3
Etiology		*Electrocardiographic Findings When Seen Initially*	
A.S.H.D.	16	Normal	1
H.C.V.D.	8	Abnormal	24
R.H.D.	1		
		Electrocardiographic Changes Since Patients Were First Seen	
Age (years)		Improved	2
Average	53	Further changes	7
Youngest	43	Essentially unchanged	16
Eldest	70		
Duration of Therapy in Months		*Myocardial Infarction*	
Average	46	Number seen as initial complaint	11
Shortest	6	Subsequent infarcts	3
Longest	122		

A.S.H.D. = Arteriosclerotic heart disease. H.C.V.D. = Hypertensive cardiovascular disease. R.H.D. = Rheumatic heart disease.

has survived 10 years and 2 months since his first episode of infarction. The patient followed the shortest period of time has been seen for 1 year. The criterion for improvement has been the decrease in either the number of daily attacks or a reduction in the amount of nitroglycerin taken, whichever was greater. If the patient's daily number of attacks decreased between one third and one half, he was considered moderately improved. A decrease in nitroglycerin (or attack rate) greater than 50 per cent or more of that of the preceding 6 months was considered marked improvement. If the attack rate decreased less than one third, the patient was considered unimproved.

As this plan evolved, it became obvious that long-acting vasodilators were of no great value in the management of angina pectoris, and that equal results could be obtained through the use of tranquilizing drugs alone. In 18 patients, meprobamate (Miltown or Equanil) was used. This compound was chosen because of the paucity of toxic effects, and the minimum amount of drowsiness produced by it. Four patients have used various rauwolfia preparations. One patient takes both Serpasil and meprobamate. Two patients, having taken Miltown for a short period, have felt so well that they now use no medication. As might be expected, the 5 patients on rauwolfia extracts are hypertensive, but the relief of the angina has not been correlated with change in the hypertension. As Table II shows, there is no significant difference in results between those receiving a vasodilator—pentaerythritol tetranitrate—and meprobamate, and those receiving the latter drug alone. Three illustrative cases are summarized briefly in order to show the bearing of the more intangible aspects of the therapy.

TABLE II. RESULTS OF THERAPY

NUMBER OF PATIENTS	VASODILATOR AND TRANQUILIZER	TRANQUILIZER ALONE	NO MEDICATION
Total	8	15	2
Greatly Improved	7	11	2
Moderately Improved	–	2	–
Unimproved	1	2	–

Per cent greatly improved	80%
Per cent showing some improvement	88%

CASE 1.—This 54-year-old retail salesman was first seen at home in December, 1951. At that time he complained of vague substernal and epigastric pain. Clinical and electrocardiographic findings were negative. On April 16, 1956, he began to notice substernal pain worse on exertion and excitement. By May, 1956, these episodes had increased so that he was taking 8 to 10 nitroglycerin tablets daily. Examination at that time revealed a blood pressure of 220/160 mm. Hg. The heart was not enlarged. Electrocardiograms revealed early left ventricular hypertrophy. The patient was started on a barbiturate preparation and Peritrate. These medications failed to relieve the angina.

In August, 1956, he developed severe substernal pain. Electrocardiograms were indicative of an acute anterior wall infarction. He was admitted to St. Vincent's Hospital and treated for 4 weeks with anticoagulant drugs.

Upon discharge the angina remained as severe and frequent as it had been prior to admission, although the electrocardiograms showed some improvement. On Oct. 27, 1957 severe substernal pain again recurred. The ECG reverted to the pattern of August, 1956, and he was readmitted to the hospital for 2 weeks.

Once again following discharge, the anginal pattern continued. Because the author knew something of the patient's business background, this was explored a bit. The patient worked in a store owned by his brother-in-law. The patient himself had no interest in the business, but had considered himself part of the management. About 3 years before the first hospitalization, and about a year before the angina started, the owner's son-in-law had entered the firm and had quite obviously, and somewhat aggressively, taken over management functions. This annoyed the patient tremendously. In conversations during several office visits, it was pointed out to the patient that he did have a good position, with excellent disability provisions, and that his job was not in jeopardy. He was urged to do his work and cease competing with the new arrival on the scene. At the same time, meprobamate was added to the regimen.

Since these conversations the patient has improved markedly. The ECG remains stable, showing an old anterior wall infarction. The blood pressure is steady at 170/110 mm. Hg. The number of anginal attacks has fallen to one or none daily. He takes only an occasional nitroglycerin tablet.

Comment.—Resentment and competitiveness, both of which had to be concealed, seem to have been a potent factor in the causation of organic heart disease and angina pectoris in this patient. His ability to make a better adjustment to his employment situation resulted in marked relief of angina pectoris.

CASE 2.—This patient is a department store owner who was first seen in the office on Aug. 31, 1953. At that time he was 58 years old. Three years earlier a subtotal gastric resection, for a bleeding peptic ulcer, had been performed. Two days before his first visit he had developed substernal pain lasting 15 to 20 minutes, accompanied by perspiration. Physical findings revealed a blood pressure of 190/90 mm. Hg. The heart was slightly enlarged. There were absent dorsalis pedi pulsations. The electrocardiogram, apart from flattening of T_{V5} and T_{V6}, was negative. During September and October, 1953, he began to have frequent episodes of angina daily, and, in September, he was admitted to St. Vincent's Hospital because of severe substernal pain. Electrocardiograms revealed small and inverted T waves in Leads I, II, and V_{4-6}. Within 2 weeks these had become upright. It was felt that myocardial insufficiency rather than infarction had occurred.

Subsequently, anginal pain persisted, and frequent hospitalizations were necessary. In fact, between the initial hospitalization and December, 1956, there were 4 hospital admissions for severe angina. Most of these were necessitated by the intense fear and apprehension which the more severe episodes generated in the patient. Upon studying the patient, it was found that there was a marked tendency for the angina to become worse about the time that the department store was busiest because of seasonal and holiday fluctuations. On Dec. 24, 1956, the author happened to observe the patient at his store, and noted that he was behaving more like a clerk than the owner. That night he was readmitted to St. Vincent's Hospital. Since December, 1956, strenuous attempts have been made to regulate his activity and to keep him off the floor of the store. He had a minor flare-up of pain in June, 1957, before Father's Day, but managed to avoid hospitalization. Under a regimen of regulated activity, the patient has only occasional anginal episodes. He is receiving meprobamate. Vasodilators have been stopped.

Comment.—This is a tense patient, from a rather tense family. His angina probably represents a combination of both emotional stress and undue physical exertion. By regulating his activity carefully, he remains fully active in his business, and pain-free.

CASE 3.—This 53-year-old produce merchant was first seen because of severe substernal pain of 24 hours' duration on Jan. 28, 1956. He stated that 2 years earlier he had been hospitalized 9 weeks for substernal pain and high blood pressure. The present pain had been severe and persistent but had been unaccompanied by perspiration or pallor.

Examination revealed a blood pressure of 190/110 mm. Hg. The heart was enlarged and a Grade 2 apical systolic murmur was present. The electrocardiogram showed T_1 to be inverted. There were QS complexes in Leads V_1 through V_3. T waves in V_4 to V_6 were inverted and the S-T complexes in these leads showed upward coving, although they were isoelectric. The patient was hospitalized at St. Vincent's Hospital for 3 weeks. Laboratory work did not confirm the diagnosis of acute infarction, and the electrocardiographic pattern did not change. Accordingly, the final diagnosis was myocardial insufficiency.

Following discharge the patient began to have rather frequent anginal episodes, about 7 daily, occurring usually on exertion but often at rest. These were promptly relieved by nitroglycerin. The use of triethanolamine trinitrate and PETN failed to relieve the patient. He continued to have severe angina through November, 1956.

This patient ran a rather active business. He had, however, three adult sons who were working with him, but to whom he delegated no important responsibilities or duties. In fact, the patient frequently drove one of the trucks himself. We then discussed the possibility of delegating more of the responsibility of the business to the sons and utilizing the patient's talents in the role of consultant, and so forth. Since then there has been a marked reduction in the incidence of angina. He now uses less than one nitroglycerin tablet daily. He still goes to his business, but is more content to sit in the background. His blood pressure remains the same, 200/120 mm. Hg. His electrocardiogram is unchanged.

Comment.—It is possible that some rivalry existed here between the patient and his children, along with some reluctance to see whether they could run the business adequately. Once the patient decided to delegate some authority and duties, his angina practically disappeared although his blood pressure and electrocardiograms have shown little if any change.

The percentage of patients greatly improved or totally relieved of pain by this approach to treatment was 80 per cent, or 20 patients. The total number showing some degree of improvement was 88 per cent, or 22 patients. These are undoubtedly high figures. But I feel they can be attained in almost any group of anginal patients if sufficient effort is made by both patient and physician along the lines outlined above.

There have been 3 failures. One is a 65-year-old man who has hypertension and cardiomegaly, plus azotemia, albuminuria, cylindruria, and anemia due to renal arteriosclerosis. It is doubtful whether he is salvageable under any plan of therapy. The second is a 47-year-old woman with combined mitral and aortic valvular diseases. She is also considerably apprehensive and has expected to die ever since rheumatic heart disease was first diagnosed in her twenties. The last is a 55-year-old presser who suffered a myocardial infarction in October, 1956. He has not returned to work, has frequent anginal episodes, and all attempts at reassurance and rehabilitation have failed.

Employability is often considered an important criterion of successful cardiac therapy. In my own experience with angina pectoris, employability is affected not only by the patient's affliction, but also by his desire to work. As Braceland[1] stated, in discussing rehabilitation in general, the patient must have motivation toward recovery and not toward secondary gains derived from prolonged disability. Thus, some of our unimproved and many of our moderately improved

patients are working. At least one of the patients is unemployed because he cannot overcome the fear of another myocardial infarct. Employability frequently depends on the attitudes and fears of the physician treating the patient and on the former's criterion for returning to activity. Table III shows the employment status of these 25 patients. Evaluation of employability in women is somewhat difficult if they are housewives. These women are considered fully employed if they perform all their household duties and lead an active social life. Those having to curtail one or the other are considered partly employed, and those curtailing both are rated as unemployed. Fifteen, or 60 per cent, of this series are fully employed. Five patients, 20 per cent, are partially employed. The remaining 5 are unemployed. However, 3 of these last patients are 65, 69, and 70 years old, respectively, and might well find themselves unemployed regardless of their cardiac status.

TABLE III. EMPLOYABILITY

SEX	FULL TIME	PART TIME	UNEMPLOYED
Men	12	2	4
Women	3	3	1
Total	15	5	5

Per cent fully employed 60%
Per cent working full or part time 80%

The fourth unemployed patient is the 55-year-old man mentioned earlier as a treatment failure. The last patient is the 47-year-old rheumatic cardiac. Surprisingly, the other treatment failure has so far managed to work full time in spite of his many disabilities. Fortunately his work does not include heavy physical activity. It is obvious that severe angina and employability are not incompatible, and employability is an inadequate criterion in evaluating therapy.

In 1935, Katz[2] stated that angina pectoris is a variable subjective manifestation with little consistent quantitative relation to the underlying coronary disease, and little correlation with the electrographic status. This would seem to be so with this series. Electrocardiograms have shown no constant pattern under therapy. The electrocardiograms of 16 patients have remained static. Two patients have shown some improvement in their tracings, probably related to the time that has elapsed since their initial myocardial infarction. The tracings of 7 patients have shown deterioration. These changes have been correlated neither with clinical improvement or employability.

Beck[3] feels that some patients with coronary atherosclerosis die because of the sudden onset of a severe ventricular arrhythmia, namely, ventricular fibrillation. The rationale for this is based on the assumption that difference of potential develops between ischemic (blue) areas of heart muscle and more vascular (red) areas of myocardium. If this were true, one might expect to see, frequently, nonlethal ventricular arrhythmias such as premature ventricular contractions, or

paroxysmal ventricular tachycardia. None of these patients has suffered such episodes, either before or after the institution of the holistic approach. In fact, there have been no arrhythmias in the entire series since coming under observation.

DISCUSSION

The search for an effective preventive of angina pectoris was probably initiated by Heberden's[4] description of the disease and has been energetically continued since. Ever since the efficacy of nitroglycerin as an abortive of precordial pain became known, much research has centered about the discovery of a preparation as efficient but more prolonged in action than glyceryl trinitrate. This has led to the use, generally followed by discard, of various nitrate compounds. Papaverine and xanthine derivatives have also been administered, with varying success, to the anginal patient. In recent years pentaerythritol tetranitrate has had wide use as a coronary vasodilator. Russek[5,6] stated that this compound has resulted in increased exercise tolerance in his patients. Feinblatt and Ferguson[7] studied the effect of PETN timed disintegration capsules in angina. They found that anginal pain was relieved within 1 hour after ingestion of such capsules. However, substernal pain lasting one hour or more is not typical of angina pectoris.

Still another nitrate, triethanolamine trinitrate (Metamine) was reported upon favorably by Fuller and Kassel.[8] Russek[9] found this compound ineffective, which finding parallels the experience of the author.

Although many reports favor PETN, there has been no marked effect noted from the use of this preparation in the present group of patients. Perhaps some light is shed on the conflicting reports of various vasodilators by the article of Evans and Hoyle.[10] These authors stated that placebos relieved pain in 38 per cent of anginal patients. In 1955, Beecher[11] described a similar percentage of pain relief (35 per cent), also with placebos. A rather recent and careful study by Cole, Kay, and Griffith[12] stated that both Metamine and Peritrate were ineffective, and that over 50 per cent of their patients showed improvement for 3 months regardless of the therapy used. The authors concluded that the most important therapeutic factor in the relief of angina pectoris was a good patient-physician relationship.

Because of the uncertainties regarding drug therapy, attention has been focused by many investigators upon the relief of anginal pain and myocardial ischemia through operative procedures. Since these rest upon the hypothesis that coronary collateral circulation is stimulated and created through operation, it might be worth while to summarize the rather complete study of the coronary circulation made by Blumgart, Schlesinger, and Davis,[13] in 1940. They found coronary atherosclerosis to be a diffuse disease involving the entire system. Few, and rather small anastomoses were found between the left and right coronary arteries in normal hearts. Many, and larger anastomotic connections were found in the hearts showing coronary atherosclerosis. The efficacy of this circulation was demonstrated by the fact that in sclerotic hearts occlusion of a coronary artery or branch did not necessarily result in infarction, and that, at times, the

thrombus was not contiguous to the infarct. Myocardial hypertrophy apparently stimulates anastomoses. Furthermore, anatomic change is not the sole determining factor in angina pectoris, for extensively diseased hearts often came from patients who had had no anginal symptoms when alive. Finally, because of the structrual changes in the artery, these authors doubted whether coronary artery spasm could be a large factor in the production of angina. It would thus appear that coronary atherosclerosis is a great stimulant to the development of effective coronary collateral circulation.

It would seem logical to evaluate surgical therapy against the background of this important and careful series of experiments. Beck[3,14-17] has introduced 2 procedures for the relief of angina pectoris. The first is the so-called Beck I operation, consisting of the introduction of asbestos particles into the pericardial cavity and the use of parietal pericardium as a myocardial graft. The second operation, the Beck II, consists of arterialization of the coronary sinus. It still remains a procedure associated with a high mortality. Furthermore, retroperfusion of blood through the sinus ceases within about 6 months postoperatively, a fact confirmed in dogs by Maniglia and Bakst.[18] Beck and the latter authors claim, however, that the operation does increase intercoronary collateral circulation. Beck states that his first procedure results eventually in the production of intercoronary anastomoses, secondary to inflammation, rather than in the production of effective anastomoses from pericardium to myocardium, However, from Schlesinger's work, it would seem that the myocardium is quite capable of stimulating its own collateral circulation.

Brofman[19] has reported the results on 225 patients treated with the Beck I procedure. He states that the operation has a low mortality, and that 90 per cent of the patients are improved, 25 per cent immediately. This statement is questionable for it is hard to see how an abundant collateral circulation can develop in such a short period. Certain groups are excluded from surgery: those with a recent history of myocardial infarction; those with congestive failure and/or hypertrophy; and those with severe hypertension. Yet, these might appear to be the patients requiring surgery most urgently.

Brofman also states that if a catastrophe is imminent, operation hastens it, a statement seemingly at variance with the report of an immediate improvement rate of 25 per cent. Finally, he states that employability of the group rose postoperatively. Our figures on employment have been stated earlier in the article, and employability in this medically treated group is quite satisfactory. It should be stressed again that employability is also a matter of the patient's motivation and the physician's direction and bears no close relation to anginal pain.

The Vineberg[20] procedure probably rests upon the rationale that creation of a hematoma in myocardial tissue will result in increased intramyocardial circulation, although the basis for such a hypothesis remains uncertain.

Most recently, ligation of the internal mammary arteries below the origin of their superior cardiophrenic branches has become quite popular, on the basis of little or no work published in the American literature. This procedure is based on the fact that, in cadavers, dye injected into these small vessels may be found in the pericardium and occasionally in the myocardium. However, pressure

differentials are nonexistent in cadavers, the only ones present being those created by the syringe of the investigator. The beating heart has a high systolic pressure. The coronary arteries do not fill in systole, when the pressure in the smaller arteries would be maximal. It is exceedingly dubious that in diastole the pressure in a small branch would exceed the diastolic pressures of even a diseased coronary artery system. In fact, in 1898, Pratt[21] stressed the importance of pressure relationships in arteries. He maintained that an artery might be terminal, not alone from anatomic relationships but simply because the resistance in the one vessel might be greater than that of the arteries with which it anastomoses. Much of the experimental data serving as the basis for the surgical approaches to therapy rests upon experiments with the dog.

While it is true that occlusion of a canine coronary can be made as complete as occlusion of the human counterpart, the normal dog lacks the shunts and passages about and below the point of occlusion which are often present in the more sclerosed human being. Great reserve, therefore, is incumbent upon the investigator transcribing results from dog to human hearts.

Perhaps because of dissatisfaction with either single dimensional medical or surgical therapy, renewed attention is being paid to the emotional aspects of angina pectoris. Anginal patients are thought by some to be a tense, rather anxious group of people. There is no evidence that such an emotional state can cause atherosclerosis, but there is some evidence that, once organic disease has occurred, angina can be precipitated by psychogenic factors. Weiss and associates[22] found a higher incidence of emotional problems in a coronary than in a control group. He also felt that some of the tension was iatrogenic. King[23] recently stated that patients with a "good psyche" had fewer anginal attacks than those who had made a poorer adjustment to coronary artery disease. This viewpoint is similar to our own and perhaps explains the benefits obtained with tranquilizers, and the great variance in response to various medicines and surgery. The helpfulness of tranquilizers and sedatives finds support in the articles of Snow[24] and Deitz,[25] who found that adding rauwolfia extracts to pentaerythritol tetranitrate resulted in increased efficacy of therapy.

At times, both physicians and patients feel that angina pectoris is a sign of impending death, or at least the premonitory signs of a myocardial infarction. However, neither is true. Although 11 of the patients reported on here were seen because they had an infarction, only 3 have developed infarctions in a period of almost 4 years.

White and Bland,[26] in 1943, reported that the mean age from the onset of angina pectoris to death was 7.9 years. Twenty-four per cent of their patients were still alive at that time and had lived an average of 18.4 years after developing angina. Robb and Marks[27] studied the survival rates in arteriosclerotic and hypertensive heart disease. Seven of 10 of their patients were alive at the end of 5 years, 50 per cent at the termination of 10 years, and more than a third survived 15 years. It would appear, therefore, that the prognosis of arteriosclerotic heart disease is thought to be more discouraging than statistics demonstrate. Also it will take some time before definitive claims concerning the value of surgical procedures can be made. Finally, it must be borne in mind that surgery itself may be a powerful placebo.

CONCLUSIONS

I have attempted to demonstrate that angina pectoris is a disease which has several components. The first is atherosclerosis of the coronary bed. The prevention or alteration of this basic pathology still lies beyond our control. Exercise, food, and particularly emotional tension may drastically affect the frequency and severity of the anginal state. Since so many variables are involved, the use of medication alone, or surgery, must be carefully and cautiously evaluated.

An approach to the problem has been presented involving primarily the lessening of occupational and emotional tension, the use of tranquilizing drugs, a close physician-patient relationship, and attempts to maintain the patient as an actively employed member of society. This has been termed a holistic approach, but it actually represents a multidimensional method that could be applied to any disease. Although this method may be unsensational, and even appear plodding, it will prove rewarding for both physician and patient. In this series it has resulted in improvement in almost 90 per cent of the patients.

At the present time, it is presented as the approach most likely to benefit the anginal patient as far as pain is concerned, and to relieve his fear and apprehension both as regards his ability to work and his outlook for the future.

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Aortic Obstruction and Cardiac Output

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The output of the heart during occlusion of the aorta has been measured by several investigators, with conflicting results. Barcroft[1] observed a slight average increase, although there was considerable variation from positive to negative changes. Hamilton and Remington[2] reported that an increased arterial pressure tended to reduce stroke volume, while Gupta and Wiggers[3] noted a definite increase in cardiac output following aortic obstruction. Barcroft further noted that if his experimental animals were vagotomized there was a constant elevation of the cardiac output following the occlusion. He postulated that a reflex was present that modified the response in nonvagotomized animals.

In view of these conflicting reports and the diverse procedures employed to measure the cardiac output, it appeared advisable to investigate this problem again, utilizing catheterization of the pulmonary artery and the direct Fick method for the measurement of cardiac output. The surgical procedures were kept to a minimum and occlusion of the aorta was accomplished by inflation of a balloon on a catheter inserted into that vessel.

METHODS

Eighteen mongrel dogs ranging in weight from 10.9 to 24.0 kilograms (mean body weight 14.9 kilograms) were used in a total of 34 experiments. The animals were anesthetized with Nembutal (30 mg./Kg. of body weight) and heparinized (5 mg./Kg. of body weight). A cardiac catheter was inserted into an exposed jugular vein and positioned either in the pulmonary artery or the right ventricle. A triple-lumen balloon cardiac catheter was passed through an exposed femoral artery and placed in the thoracic aorta so that the balloon was at the level of the fourth intercostal space. Obstruction was accomplished by inflation of the balloon with 4 ml. of saline. Complete occlusion was confirmed by a precipitous drop in femoral arterial pressure to below 16 mm. Hg.[4] All occlusions were maintained for 5 minutes. Blood pressures in the aorta both above and below the balloon and in the pulmonary artery or right ventricle were measured throughout the experiment with Statham strain gauges and appropriate amplifying and recording equipment. Total oxygen consumption was measured with a Benedict-Roth metabolism apparatus. Blood samples were drawn simultaneously from the aorta above the balloon and the pulmonary artery, for the determination of oxygen content by the method of Van Slyke and Neill.[5] These blood samples were drawn during the control period, 1 minute after occluding the aorta, 4 minutes following occlusion, and both 1 minute and 5 minutes after the obstruction was released. Cardiac output was calculated by the direct Fick principle.

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In 13 of the experiments atropine (0.5 mg./Kg. of body weight) was given intravenously following the control cardiac output. Twenty minutes were allowed for the atropine to take effect before the aorta was obstructed. Cardiac output determinations were made on 6 of these experiments and on 17 of the experiments in which no atropine was given. Upon completion of each experiment, the incisions were sutured and the animal was given 300,000 units of penicillin intramuscularly and returned to its cage.

Statistical analysis of the data was conducted by the paired sample technique and the "null" hypothesis was rejected at the 5 per cent level.

RESULTS

All animals survived a total obstruction of the aorta for 5 minutes, and no residual effects were observed. The hemodynamic variations observed in the aorta above and below the obstructing balloon and the changes in heart rate values are similar to those previously reported.[4] The mean aortic pressure rose from a control value of 134 mm. Hg to a maximum of 169 mm. Hg following the occlusion. The pressure in the femoral artery fell to approximately 10 mm. Hg and remained constant at this low level during the period of interference with normal blood flow distribution. Heart rates fell slightly and remained at this low level throughout the obstruction period. A transitory hypotension was noted following the release of the obstruction. Responses similar to the abover both in duration and degree, were observed in those animals given atropine prio, to aortic occlusion. The changes in pulmonary artery systolic and diastolic pressures were significantly increased statistically during the entire occlusion period (Table I). Atropinization of the animals did not induce any significant changes in pulmonary arterial systolic pressures. However, when the aorta was occluded on these atropinized animals, the pulmonary artery diastolic pressures

TABLE I. ALTERATIONS IN PULMONARY ARTERIAL PRESSURES AS A CONSEQUENCE OF TOTAL OCCLUSION OF THE THORACIC AORTA AT THE FOURTH INTERCOSTAL SPACE

	UNTREATED		AFTER 0.5 MG./KG. OF ATROPINE	
	SYSTOLIC (MM. Hg)	DIASTOLIC (MM. Hg)	SYSTOLIC (MM. Hg)	DIASTOLIC (MM. Hg)
Control	15.4	7.9	20.3	8.7
Occlusion of Aorta				
1 minute	20.6*	9.8*	22.6	11.4*
2 minutes	18.8*	8.8*	19.4	10.5*
3 minutes	20.1*	8.3*	21.2	11.7*
4 minutes	19.2*	8.7*	20.9	9.8
5 minutes	17.9*	9.0*	20.5	9.7
Release of Occlusion				
1 minute	18.0*	7.8	20.4	8.1
2 minutes	16.2	8.6	19.2	7.9
5 minutes	15.8	8.6	20.4	8.1
10 minutes	16.0	7.8	20.2	8.0

*Significantly different from control at 5 per cent level or better.

TABLE II. VARIATIONS IN CARDIAC OUTPUT AND ASSOCIATED FACTORS AS A CONSEQUENCE OF A 5-MINUTE OBSTRUCTION OF THE THORACIC AORTA AT THE FOURTH INTERCOSTAL SPACE

	CONTROL	1ST MINUTE OBSTRUCTION	4TH MINUTE OBSTRUCTION	1 MINUTE AFTER RELEASE	5 MINUTES AFTER RELEASE
Untreated Animals n = 17					
Arterial Oxygen Content, vols. %	18.09	18.89	18.21	20.04	19.49
t = difference from control		1.17	1.21	0.53	0.98
Arterial Mixed Venous Oxygen Δ, vols. %	3.83	3.27	4.46	4.53	4.24
t = difference from control		1.78	1.61	1.25	1.54
Oxygen Consumption, ml./min.	89	70	92	103	93
t = difference from control		4.6*	0.2	2.9*	2.7*
Cardiac Output (L./min.)	2.47	2.34	2.30	2.33	2.20
t = difference from control		0.66	0.30	0.16	0.80
Animals Given 0.5 mg./Kg. Atropine I.V. n = 6					
Arterial Oxygen Content, vols. %	18.28	18.78	19.07	19.23	19.38
t = difference from control		0.98	1.23	1.47	2.24
Arterial Mixed Venous Oxygen Δ, vols. %	2.90	2.97	3.96	4.30	4.31
t = difference from control		0.34	2.93*	3.50*	2.74*
Oxygen Consumption, ml./min.	81	78	71	86	85
t = difference from control		0.3	1.4	1.0	1.2
Cardiac Output (L./min.)	2.80	2.68	1.81	1.97	2.08
t = difference from control		0.39	2.07	2.77*	1.94

*Significantly different at 5 per cent level or better.

were significantly increased during the first 3 minutes. In those dogs, either control or atropinized, in which right ventricular rather than pulmonary artery pressures were recorded a pattern of response similar to the above was observed.

The variations in cardiac output and associated factors following aortic occlusion are presented in Table II. Cardiac output determinations made during the occlusion did not differ appreciably from control values in either group of animals. The cardiac output in the atropinized animals tended to fall during the obstruction; however, the change was not statistically significant. This decreased output persisted following the release of the occlusion and was significantly lower statistically than the control value during the first postocclusive minute.

The oxygen consumption in the nonatropinized animals was significantly decreased 1 minute after the aorta was occluded, had returned to control levels in 4 minutes, and was significantly increased 5 minutes after the release of the obstruction. Oxygen consumption of the atropinized animals was not altered as a consequence of aortic occlusion. Atropinization of the animals resulted in a significant decrease in the arterial-mixed venous oxygen difference. This was not due to alterations in the saturation of arterial blood. However, because of the slight fall in total oxygen consumption, the cardiac output remained essentially normal.

Calculations of cardiac work and total peripheral resistance did not reveal any statistically significant differences, primarily because of wide individual variation. Both of these parameters tended to show slight increases during the occlusion period and slight transitory decreases in the first few minutes following release of the obstruction. The changes in total peripheral vascular resistance during occlusion were more marked and consistent in the atropinized animals.

DISCUSSION

The general effects of acute aortic occlusion on the cardiovascular system were somewhat similar to those reported earlier.[1-4,6,7] Observations on heart-lung preparations by Anrep and Bulatar[8] demonstrated that pulmonary arterial pressures increased almost proportionately to the systemic pressure rise following occlusion of the aorta. These findings were not confirmed by Katz and Wiggers,[9] who reported insignificant changes in pulmonary arterial pressures in intact dogs following this procedure. The slight increases were attributed to the improved right ventricular output consequent to increased coronary flow. Allbaugh and Horvath[4] have shown, however, that blood continues to flow from the inferior vena cava during the entire period of obstruction; this would be a more potent factor to right heart output than the slight contribution by the coronary circuit. Furthermore, the present data confirm the earlier observations of Anrep and Bulatar,[8] in that a significant rise in pulmonary arterial pressures does occur; however, this increase is not of the same magnitude as suggested by those investigators. A rather perplexing finding was the lack of such an elevation in the atropinized animals. Since the cardiac output did decrease somewhat in these animals, the increased pulmonary pressures in the nonatropinized animals might

be attributed to back pressure effects. Further investigations are required to determine the exact mechanism of this effect.

Sudden occlusion of the thoracic aorta did not appreciably alter the cardiac output. The slight increase noted was statistically insignificant. Although Barcroft found a much greater mean increase (10 per cent) in cardiac output than was evident in the data being presented, 4 of his animals demonstrated no change, 5 exhibited a decrease, and the remaining 4 had marked elevations. The variable results reported by other investigators[2,3] can be explained as falling within the vagarities of response observed by the present authors and by Barcroft.[1] The latter investigator credited this variability to the participation of a reflex, fibers in the vagus nerve, which sometimes prevented the anticipated rise in cardiac output. After sectioning the vagi, Barcroft found a consistent elevation of the cardiac output upon occluding the thoracic aorta. However, in the current study, atropinization did not lead to similar results. On the contrary, there was a tendency for the cardiac output to fall during the period of occlusion. Upon release of the occlusion, the cardiac output remained low. Blalock,[6] occluding the aorta for a much longer time than had been usually employed, observed a marked fall in cardiac output. The maintenance of the normal cardiac output was related to the constancy of the A-V_{O2} differences and the oxygen consumption. No explanation is available for the lack of change in oxygen consumption; considering the mass of tissue utilizing oxygen, a decrease would have been anticipated.

It is perhaps suggestive that neither Barcroft,[1] Brotchner[7] nor the present investigators have found that vagotomy or atropinization interferred with the elevation of the aortic pressure following occlusion of this vessel. Similarly the bradycardia consequent to occlusion is not interfered with by prior atropinization of the experimental animals. The reflex mechanism as postulated by Barcroft[1] did not occur; in fact, if there was such a mechanism it operated in the reverse, and possibly more physiologic, direction.

Sudden occlusion of the thoracic aorta at the position described decreases the size of the vascular bed by some 50 to 60 per cent. Since some collateral circulation to the posterior segment of the body is known to occur,[4] the reduction in the effective vascular bed is probably not this great. Nevertheless, the maintenance of a normal or slightly diminished cardiac output during the occlusion represents a relatively great increase in blood flow to the remaining arterial bed. Since neither cardiac work nor total peripheral resistance changed significantly, the state of the heart is apparently no different than in the nonobstructed state. However, for the size of the perfusion bed now involved, these are appreciable changes which undoubtedly indicate some degree of stress. The explanation for this elevated cardiac output is not too clear at present. Barcroft[1] explained his increased outputs on the basis of a very small quantity of blood flowing into the upper circuit from the inferior vena cava during the early part of the occlusive period. Previously reported results[4] indicate that the volume of this flow is much greater than Barcroft's data suggest and that, furthermore, this flow is maintained during the period of aortic obstruction. Consequently, the increased output cannot be explained on the simple basis of increased circulating blood

volume. That the latter is partially responsible is suggested by some crude calculations indicating that about 70 to 75 per cent of the total blood volume is circulating through the upper circuit following the obstruction. The most plausible remaining possibility lies in the necessity of maintaining the cardiac output at this level in order to overcome the increased peripheral resistance. Why there should be an increased resistance is not too clear. Naturally, some resistance is offered by the collateral circulation that has been demonstrated to exist to the lower segment of the aorta.[4] This mechanical factor is probably too small to account for the pressure rise observed, and, furthermore, the elevation of the upper aortic pressure occurred too rapidly for these anastomotic connections to exhibit their influence. The situation existing in complete obstruction to flow is not similar to that observed in coarctation of the aorta where pressures can become elevated because of increased hindrance to flow through the constricted segment of the aorta and the presence of collateral circulating pathways. Neither can pressor humoral agents elaborated consequent to reduced renal blood flow account for this phenomenon. Both the time factors and the rapidity of establishment of normal pressures following release of the obstruction are against the involvement of any renal anoxic theory.

SUMMARY

Sudden complete occlusion of the thoracic aorta at the level of the fourth intercostal space resulted in a marked rise of aortic pressure above the occlusion, an elevation of pulmonary arterial systolic and diastolic pressures, a slowing of the heart rate, and essentially no change in cardiac output. This latter effect is somewhat spurious since the same cardiac output was now being delivered to a much smaller vascular bed. Therefore, it represented effectively an increase in the cardiac output for the prevailing situation. Atropinization of the experimental animals prior to the induction of the occlusive episode did not alter the pattern or degree of response except in two particulars, i.e., little change in pulmonary arterial pressures and a tendency for the cardiac output to decrease. The adjustments following release of the occlusion were similar in both groups of animals, with the exception of a significant fall in cardiac ouput during the first postrelease minute in the atropinized animals.

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Ostium Primum

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While atrial septal defects of the ostium secundum type are frequent, those of the ostium primum type are relatively rare.

It is our purpose to report an unusual case of ostium primum in a 62-year-old man who had, in addition, stenosis of the aortic valve, myocardial infarction, and pulmonary and myocardial tuberculosis.

CASE REPORT

This 62-year-old white male farmer began to complain of shortness of breath in 1954, approximately 3 years prior to his last admission to hospital and his death. During his first year of illness he was treated by his family physician with Mercuhydrin. In 1955, he was admitted to the V. A. Center because of shortness of breath. There was no history of rheumatic fever.

Physical examination on his first admission in 1955, showed a well-nourished white man. The blood pressure was 180/110 mm. Hg. Circulation time with Decholin was 17 seconds, and with ether, 4 seconds. Venous pressure was 10 cm. of water. The heart was enlarged to the left. A systolic thrill was felt in the pulmonic area, and there was a loud, harsh, Grade 4 systolic murmur over the pulmonary area. The pulmonic second sound was markedly accentuated and slightly split. There was some suggestion of clubbing of the fingers and toes.

X-ray of chest showed right auricular, right ventricular, and left ventricular enlargement and hyperemic lung fields. The aorta was elongated and tortuous, with calcification in its arch. The ECG showed left axis deviation, right heart enlargement, and ventricular premature contractions. A congenital heart disease, probably an atrial septal defect, was considered, but the patient did not agree to cardiac catheterization. He was digitalized, with a satisfactory response, was discharged, and was well for 2 years. He was able to do farm work until a few weeks prior to his second admission when he again became dyspneic.

On his second admission in 1957, the patient was in extremis and markedly cyanotic. Moist râles were heard over the lung fields. The liver extended to the umbilicus and was tender. There was massive edema. The heart sounds were very distant.

Post-Mortem Examination.—The heart weighed 1,000 grams. The valve orifices measured as follows: tricuspid 17 cm., pulmonic 10.5 cm., mitral 13 cm., and aortic 6 cm. The left ventricle was 15 mm. in thickness and the right measured as much as 13 mm. (Fig. 1). The heart showed marked enlargement, and the right ventricle and atrium were disproportionately increased in size. The left auricle was not enlarged. The myocardium was firm in consistency. Cut sections through the anterior septum revealed a few mottled and hyperemic markings grossly producing the picture of a recent infarct.

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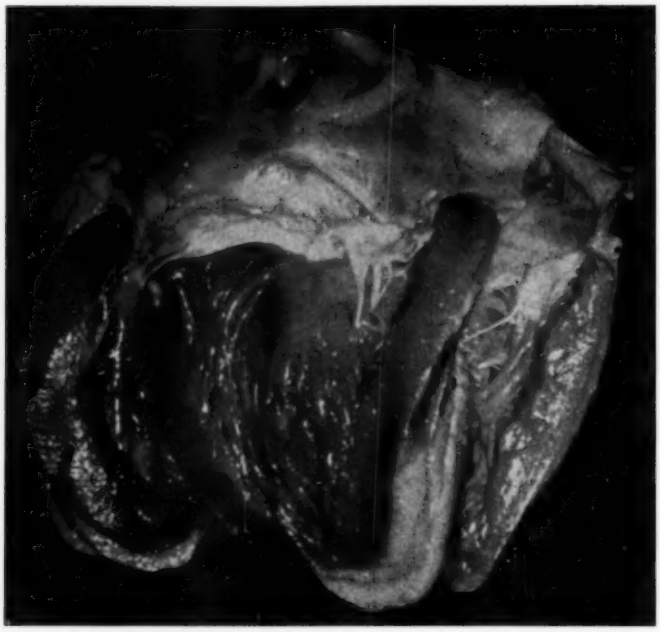

Fig. 1.—Note relative thickness of right and left ventricles.

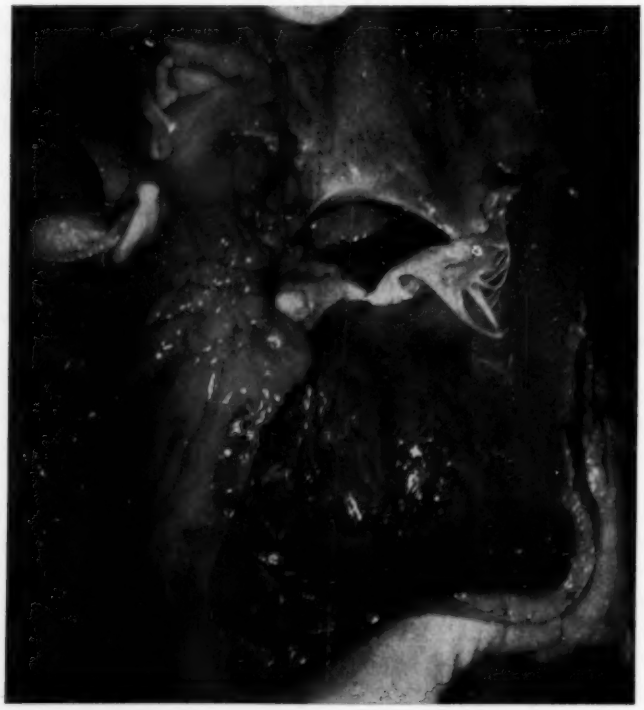

Fig. 2.—Ostium primum, view from left ventricle.

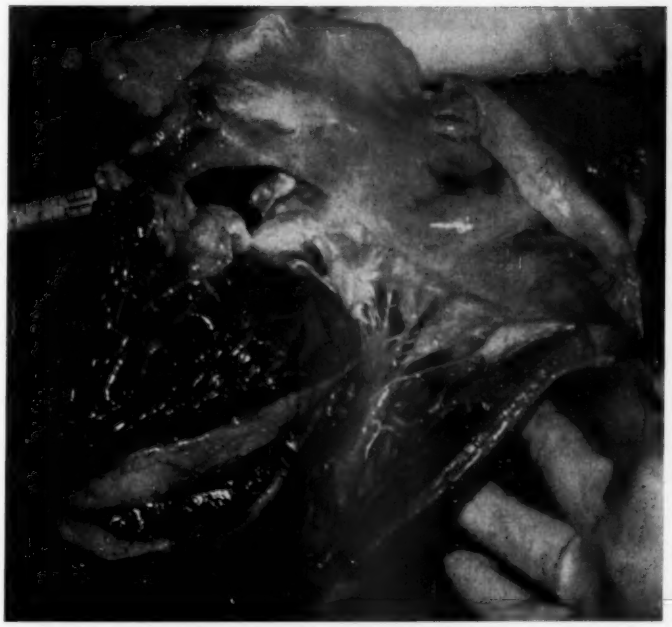

Fig. 3.—Ostium primum, view from right ventricle.

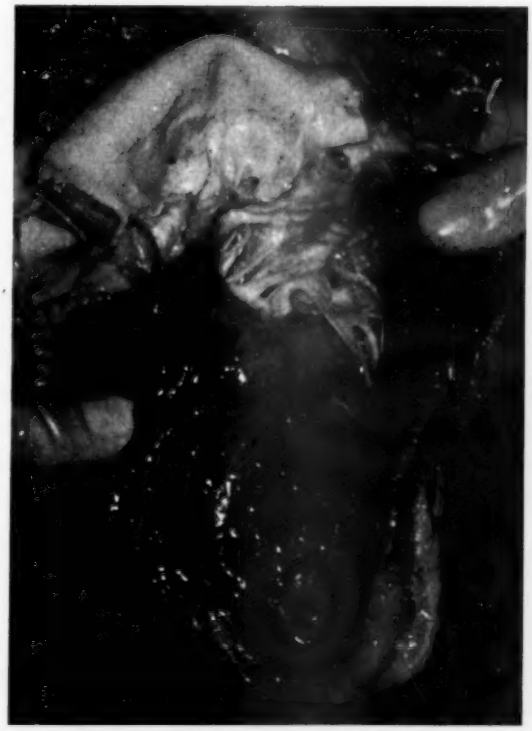

Fig. 4.—Stenotic aortic valve.

Located in the interatrial septum was a defect measuring 3.5 cm. in diameter. Anatomically, it lay just superior to the insertion of the mitral and tricuspid valves. The foramen ovale was anatomically closed and located above, and independent of, the defect. The mitral and tricuspid valves were intact and demonstrated no appreciable thickening. There was no cleft mitral or tricuspid valve present (Figs. 2 and 3). The aortic valve showed fusion of two of the cusps, with considerable deposition of calcium throughout producing a degree of rigidity and stenosis (Fig. 4).

The coronary arteries showed mild diffuse atheromatous changes, and at one level the lumen of the anterior descending branch was filled with a recent thrombus. A cut section through the region of the anterior septum revealed mottled and hyperemic markings, producing the picture of a recent infarction. The lungs showed throughout the parenchyma innumerable small, firm areas averaging 6 cm. in diameter, which on cut section showed mottled grayish scar tissue. The pulmonary vessels were large and free from thrombi.

Microscopic Examination.—Sections from the recent myocardial infarct showed characteristic coagulation necrosis. Also, located in the myocardium were small granulomas, consisting of lymphocytes and giant cells, and a few epithelioid-like cells. No Aschoff bodies were demonstrated.

The lungs showed small tubercles consisting of epithelioid and giant cells. There were numerous lymphocytes present. Several acid-fast bacilli were demonstrated by Fite's stain in one of the lymph nodes. The pulmonary vessels showed moderate sclerotic changes.

DISCUSSION

Ostium primum defect of the atrial septum is usually, but not always, associated with incomplete division of atrioventricular canal. Some authors divide these conditions into two separate categories.[1] Others consider this unnecessary, and include all these cases under the same caption of "ostium atrioventriculare commune."[2] All gradations can occur, from cases like ours with ostium primum without ventricular septal defect and intact A-V valves to a complete atrioventriculare commune.[3,4]

Longevity in patients with atrial septal secundum type defects without associated anomalies is not unusual.[5] Longevity in cases of atrial septal defects of the secundum type with Lutembacher's syndrome,[6] and in cases of the ostium primum type with Lutembacher's syndrome have been reported.[7] Longevity in patients with ostium primum defects without associated anomalies is rather rare; usually such patients die in infancy.[2]

Association of ostium primum with Lutembacher's syndrome with acquired syphilitic aortic insufficiency occurs infrequently.[8,9] However, to our knowledge, no case of ostium primum defect without Lutembacher's syndrome and with an associated acquired calcific aortic stenosis has been reported.

The pulmonary tuberculosis was an accidental finding in our patient. The immediate cause of his death was the thrombosis of the coronary artery with myocardial infarction. Tuberculous myocarditis, which is rather rare,[10] was also present in this patient, and it is quite possible that it might have been a contributing factor in the fatal outcome of the myocardial infarction. Furthermore, this case is also proof that hyperemic lung fields do not always protect the patient from pulmonary tuberculosis.

It is amazing that the patient, with this large defect in the atrial septum, had lived to the age of 62. Without any difficulty he had done heavy farm work all his life. As far as we could ascertain, no similar case has been described of a patient with ostium primum without cleft mitral valve, who lived to the age of

62. Nor to our knowledge has there been any case report of a congenital atrial septal defect of the ostium primum type with acquired aortic stenosis. It has to be postulated that those two lesions are purely coincidental.

SUMMARY

In summary, this 62-year-old man had an ostium primum, marked right ventricular hypertrophy, a calcific aortic stenosis, pulmonary and myocardial tuberculosis, and, as a final episode, a myocardial infarct.

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Book Review

VIRUS DISEASES AND THE CARDIOVASCULAR SYSTEM. By Ernest Lyon, New York, 1956, Grune & Stratton, Inc., 215 pages. Price $5.75.

Very little concrete information is available about the effects of viruses upon the cardiovascular system. This book attempts to review the subject in a comprehensive manner. In terms of current virology it is uncritical, diffuse, and not up to date. For the clinician not familiar with the field, a critical, interpretive account of the subject would be of far more value.

D. H.

Announcements

THE NORTH AMERICAN CHAPTER of THE INTERNATIONAL CARDIOVASCULAR SOCIETY will hold its meeting at the Sir Francis Drake Hotel, San Francisco, Calif., June 21, 1958. Address: Dr. Henry Haimovici, Secretary, 105 E. 90th St.. New York 28. N. Y.

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its SEVENTH ANNUAL MEETING at the Chase-Park Plaza Hotel in St. Louis, Mo., May 20 to 24, 1958, according to an announcement of Dr. Gabriel F. Greco, Ozone Park, New York, member of the Publication Committee. The general topic will be "Metabolism of the Heart in Health and Disease."

The scientific program will consist of symposia, panel discussions, fireside conferences, and lectures on clinical and basic research in cardiac metabolism, with particular emphasis on cardiac hypertrophy, effects of exercise and physical stress on cardiac function. Modification by disease will include particularly the possible alterations in metabolism through surgery in acquired and congenital heart disease. Prominent cardiologists from regional and national universities will participate in the program. Dr. George R. Meneely, Nashville, Tenn., will preside, with the joint cooperation of Dr. John S. LaDue, New York, Chairman of the Scientific Program, Dr. Seymour Fiske, New York, General Convention Chairman, and Dr. Edward Massie, St. Louis, Mo., Chairman in charge of local arrangements. Distribution of programs will be made upon request through Dr. P. Reichert, Secretary, Empire State Bldg., New York 1, N. Y.